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BACTERIOPHAGE WITH SPECIAL REFERENCE TO PLAGUE AND CHOLERA.*

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Death, Recovery, Immunity and the Bacteriophage.

If we consider the bacteriophage as a parasite of the bacterium, the bacterium as cause of infectious disease, and immunity as resistance of the higher organism to the growth and development of the bacterium, we can state with D'HERELLE in very simple terms the significance of death, recovery and immunity to disease. The cholera vibrio or the plague bacillus invade the human being and the result of their growth is disease followed by death or recovery. This issue " is not dependent upon a phenomenon of immunity as hitherto believed but upon the behaviour of the bacteriophage " (D'HERELLE 1927). The argument for the correlation of the presence of bacteriophage and recovery may be exemplified by cholera cases—cases with no bacteriophage present all die ; cases with feeble bacteriophage, which disappears, also die ; cases with strong bacteriophage at the outset recover promptly : cases with weak bacteriophage, which increases in potency, recover with some delay, as also may cases with fluctuation of potency (D'HERELLE and MALONE, 1927.) With recovery a period of immunity to the disease is acquired. In the same way as the bacterium makes its invasion so the bacteriophage invades the bacterium and again the result is death or recovery—of the bacterium. Immunity of the bacterium to the bacteriophage is consequent upon recovery and it becomes resistant to lytic action. Such a bacterium may be lysogenic or it may be non-lysogenic. Lysogenesis by a bacterium is explained as a symbiosis between phage and bacterium. Much of this explanation is one of analogy especially in this matter of symbiosis. It affords a basis, however, for an explanation of the characters of disease in terms of bacteriophage. Much would depend for the substantiation of the theory upon findings which were in agreement with it. This has not always

* Continued from p. 342.

been the case. PONS (1932 a) who injected bacteriophage in plague (in man and animals) could find no parallelism between its persistence in the organism and the progress of infection. The infection might be fatal even though bacteriophage was demonstrable during the whole course of the disease and even at death. But the phage theory has been further extended. According to D'HERELLE the lysin produced by the phage is identical with the familiar "opsonin" of the sero-cellular theories of phagocytosis, while acquired immunity is the result of the distribution of the lysed products of the infecting bacterium throughout the body. This is a composite explanation which incorporates, with the new conception of bacteriophage activity, all that has been contended for in the past, from the time of METCHNIKOFF and EHRLICH to the time of WRIGHT, regarding active immunization. The addition of an indirect action for the phage is necessary to explain a durable acquired immunity, as otherwise it would necessitate exposure to frequent reinfection. In D'HERELLE's own words:—"The action of the bacteriophage within the body is therefore very complex: it is the primary factor in recovery and it is the indirect agency of acquired immunity." The argument really is founded on the nature of the phage. It affords the basis for curative and prophylactic treatment of disease and the explanation of death or recovery.

But this subject of the relation of the phase or stage of a disease to the bacteriophage is not yet exhausted by a consideration of death, recovery and acquired immunity. There is still the chronic disease condition to be accounted for. D'HERELLE's own explanation is that in such a case we are dealing with symbiosis between the causative organism and the bacteriophage. The organism which is entirely free from an accompaniment of phage is called "ultrapure." Acute diseases are due to ultrapure bacteria, that is, to "normal healthy bacteria which have not been parasitized by the bacteriophage, while the chronic diseases on the contrary are due to the bacterium-bacteriophage symbiosis." The conjunction results in the attenuation of the virulence of the bacterium, which, however, has contracted an immunity, a power of resistance to the bacteriophage. "With the cholera vibrio," says D'HERELLE "all virulence becomes lost under these conditions." DOORENBOS (1932) claims to have settled the controversy over the relationship of the *V. cholerae* to the *V. El Tor* by showing that the latter is the cholera vibrio "contaminated" with phage. The organisms of the carrier state, for example *Bact. typhosum* causing a chronic infection such as cholecystitis, would presumably be another example of this symbiosis. "The bacillus isolated at the beginning of the acute disease is ultrapure while that found in the chronic condition has established a symbiotic relationship with bacteriophage." The various chronic diseases caused by *Bact. coli* and the chronic osteomyelitis of a staphylococcus are described as instances of this symbiosis. Not even tuberculosis is excluded. We may suppose then that chronic plague as found in rats may also be of this same category, and possibly also that the organism *Past. pseudotuberculosis rodentium* is not merely a rough variant of *Past. pestis* (ZLATOGOROFF and MOGHILEVSKAIA, 1928) but a plague bacillus in symbiosis with bacteriophage. Many instances of such possible explanation for the specific existence of some at least of the "allied organisms" which constitute any group of bacteria will occur to the reader.

Although D'HERELLE is insistent on the intestinal origin of phage, he ascribes the phenomenon of death or recovery in diseases which are

not intestinal to the same agency. "Recovery in plague is the same as that in the intestinal diseases." Bacteriophage "is capable of passing into the circulation and of inducing bacteriophagy in the fluids and in the organs."

Thus we see that the theory of the bacteriophage embraces a complete and consistent theory of acquired immunity. Is natural immunity also included ?

Epidemiology and the Occurrence of Bacteriophage in Nature.

We have only to continue the hypothesis, or rather D'HERELLE's hypothesis, of the relation of the bacteriophage to disease, which we have just considered, to obtain an equally simple explanation of the phenomena of the epidemic spread of disease and the termination of that spread. The mechanism of the phenomenon may be illustrated from the case of cholera and again we quote, or adapt, the argument of D'HERELLE. Cholera vibrios are introduced into a village or a district and become distributed. An epidemic results by transmission from case to case, or by one of the commonly named agencies, water, milk or flies (D'HERELLE and MALONE, 1927). "The first cases are usually fatal. Then a patient recovers through the mechanism already discussed. From this convalescent bacteriophage, 'adapted' to the destruction of the cholera vibrio, is spread throughout the environment and the recoveries become more and more frequent, the epidemic finally ending when the bacteriophage has become widely disseminated." Recovery is called "contagious" because it is due directly to dissemination of phage. It is evident that the spread of phage in a locality must be rapid and, within limits, it must come to be ubiquitous. According to ASHESHOV, in a hospital where phage is being administered to cholera cases "everything in the hospital—utensils, linen, hands of attendants—were harbouring the bacteriophage, which easily contaminated the newcomer." On this basis the convalescent in cholera, who contaminates well or river water, is a benefactor and not a malefactor towards his neighbours. In the convalescent, at a stage preceding actual cure, we have the cholera-destroying phage at the height of its potency, having become more or less completely "adapted" to, that is dominant over, the strain of cholera vibrio concerned in the epidemic. It takes time for adaptation to occur and during that time the epidemic spreads. From the point of view of the vibrio, not the phage, a point to be considered, which is said to be important for the continuance of an epidemic (ASHESHOV, 1931, p. 143), is whether the vibrio concerned is a "good" or a "bad" vibrio, that is, susceptible, resistant or unsuitable. In the first case phage becomes quickly adapted to it and is enhanced in virulence, whereas in the second case the phage loses its virulence. "This may explain why some epidemics quickly subside while others persist for a long time." Still another viewpoint is to be mentioned in connexion with the epidemic spread of cholera, dependent on the change in character of the vibrio which has become resistant to phage. With the development of resistance other characters alter. Such a vibrio, the vibrio of the secondary culture, whether *in vitro* or *in vivo*, may lose more or less of its virulence and so its capability of maintaining an epidemic. The course of a cholera epidemic is a struggle between vibrio and phage for dominance.

In the "plague" of the water buffalo, which has a causative organism allied to the *Past. pestis*, it is the occasional animal which may

recover that disseminates a bacteriophage of enhanced potency: water buffaloes ingesting it are protected from the disease.

Some of our older epidemiological ideas regarding prophylaxis and immunity require to be re-examined in the light of the phage theory. HANKIN (1896), we may remember, contrary to all hygienic notions recommended the drinking of Ganges water in preference to well water as a preventive of cholera; this receives some support now from the phage theory, which is supposed to provide an explanation of its vibriocidal properties. Again we are familiar with the relative immunity of the Bombay rats to plague as compared with the Madras rats, an immunity which has hitherto been ascribed to the development of a resistant race of rats by a process of selection under the stress of long continued incidence of plague in the one place and its absence in the other, but which might have been a matter of the type of intestinal phage present in the two rat populations. AVARI, however, was not able to find a phage virulent for *Past. pestis* in either Bombay or Madras rats. Rats on the other hand, which had become sick and recovered from plague inoculation afforded highly potent phage from the intestinal contents and from the spleen. The occurrence of much so-called simple diarrhoea at the time of a cholera epidemic is a well known epidemiological phenomenon, and here we might expect the stools of such cases, considered to be in reality mild cholera, would furnish a cholera phage, such as is obtained from the truly convalescent cholera case. CIUCA (1923), however, could not demonstrate the existence of vibriocidal phage although the phages which were obtained showed high activity for both *Bact. coli* and *Bact. dysenteriae.* It has to be remembered, of course, that an "adapted" phage is only found at a particular stage of illness, that especially associated with convalescence, and not after actual cure. These several negative instances, then, need not necessarily be taken as opposed to the phage theory, for much depends in this theory on the dissemination of, the character of, and the time of examination for, phage. One might even speculate on the possibility of a phage which had once become "adapted" to plague or cholera remaining thereafter more easily adaptable than before to either of these diseases, even if it did revert to the ordinary intestinal type. We may refer in this connexion to the doctrine enunciated by HARVEY and IYENGAR (1928) and expressed in the phrase: "Once immunised always immunised." A wide dissemination of specific phage is especially to be expected in times of epidemic. It is to be found associated with everything, water, soil, dust and flies, which are liable to excremental contamination. Such contamination with phage should then be present at all times, but then this phage would be unadapted to the causal organism of an epidemic disease. Even on the assumption of want of adaptation it is a little difficult to account for the pronouncement of FLU (1923) that the self purification of water commonly ascribed, after EMMERICH, to protozoa is independent of the action of phage, can take place in the absence of phage and is not accelerated by the presence of phage. KHAN (1930) definitely rejects any bacteriophage agency as accounting for the vibriocidal action of Ganges water. FLU (1927) records the isolation of a phage from canal water at Leyden which was active not only against *Bact. coli* and *Bact. dysenteriae* (Shiga) but also against *Past. pestis.* One might have expected that the well waters of villages in times of epidemic cholera would have shown some evidence of the presence of phage. It is surprising therefore to learn (GRAHAM, 1930) that systematic

search for the cholera phages in the well water before, during and after a cholera epidemic have been fruitless. Such are a few of the questions arising out of this discussion of the bearing of bacteriophage theory upon epidemiology and the occurrence of bacteriophage in nature, so far as they relate to cholera and plague.

Preparation and Use of Bacteriophage.

Great hopes have been raised of the therapeutic use of bacteriophage and these may still come to fruition though probably with considerable modification. According to BURNET (1930) " an active specific phage possesses all the attributes of the theoretically ideal internal antiseptic. It has no action on any living tissue, kills the invading organism rapidly and increases in amount as it does so." GRENET and ISAAC-GEORGES (1928) consider that we are already in the domain of phago-therapy for dysentery and staphylococcal affections and that we are on the point of entering this domain for plague and cholera. Unfortunately the method has not yet been sufficiently elaborated or for the matter of that critically tested to enable us to pronounce that cure or prevention in any disease has really been effected. In saying this we must be understood to refer to the direct action of phage in destroying the bacteria of disease and to exclude the immunizing action of bacteriophage lysates. Such lysates may have a distinct value as non-toxic, purely bacterial vaccines (BURNET, 1930, and LEDINGHAM, 1932, p. 469, *cit.* BUCHANAN). They have been used prophylactically in experimental plague by FLU (1929 a, b) with very considerable success and, most important, without local and general reaction. BURNET (1930 a) regards the clinical reports of the use of phage as uncritical and the results for the most part as inconstant. FLU (1923) found that phage had little effect on the self purification of water, a finding not quite in accord with HANKIN's (1896) idea of the vibriocidal action of Ganges river water. Cholera cases were treated with phage by SOUCHARD (1930) and a mortality of 24 out of 27 resulted. These cases, however, were not treated early in the disease. SEIFFERT (1925) speaks of the bitter disappointment of the original expectations from the use of phage in infectious diseases but with a recommendation to further efforts. NOBECHI (1926 b) could not effect the disappearance of cholera vibrios from the gall bladder in carrier rabbits even after the intravenous injection of 3 cc. of bacteriophage. VIOLLE and ROURE (1925) speak of poor results in the therapeutic action of phage but do not conclude finally that it is inefficacious. A more specific bacteriophage or an auto-bacteriophage may be required. MUNTER and BOENHEIM (1925) have not obtained any certain results in the coli cystitis or the dysentery of children. Most of these trials have had no satisfactory controls with which to make comparison. TOPLEY and WILSON and again TOPLEY, WILSON and LEWIS (1925), however, used bacteriophage in a strictly controlled experiment on the spread of mouse typhoid. Their observations " do not suggest that the presence of the bacteriophage will in itself prevent the epidemic spread of infection, check an epidemic when it has once started, or appreciably reduce the mortality among the population at risk." COMPTON (1928) in a very small series of animals obtained indifferent results for experimental plague. FLU (1929 c) and Harvey PIRIE (1929) confess to little evidence in animals for prophylactic or therapeutic effect. NAIDU and AVARI (1932) seem to have had little success even with a powerful pestiphage of local origin in either animal or human plague. One would scarcely

expect benefit in pneumonic plague. D'HERELLE'S own commentary on the failure of treatment of bubonic plague in India, as contrasted with his successful use of phage (4 cases) in Egypt is very interesting :—" It is possible that the differences in the results may be due to the fact that, for the cases in India, the bacteriophage employed was six or seven weeks old. But I am inclined to think that the reason for this failure is really due to the fact that the bacteriophage employed was not sufficiently potent to deal with the *strains of B. pestis in India which seem to be extraordinarily virulent*" (NAIDU and AVARI, 1927, p. 106). All workers have emphasized the necessity of using a polyvalent potent phage and for the most part use the argument of non-fulfilment of this requirement as explanation of the failures of others. TAYLOR (1930) is very emphatic that bacteriophage is " not an essential agent of recovery," and that its therapeutic administration did not influence the progress of cases of cholera, " although this phage was capable of lysing the vibrios isolated."

While we are making reference to these various trials and incidentally to the necessity for the controlled type of trial, we may note the excellent idea of D'HERELLE to establish a coefficient for each system of a disease by means of which the effect of medication may be measured. The symptoms which he takes for this purpose in cholera are : number of rice water stools, vomiting, density of the blood, cramp, collapse, anuria, pulse, and general condition. But it is advisable to pause before accepting a doctrine of inutility of treatment by phage. D'HERELLE himself has been foremost in pointing out the difficulties of phage therapy and the requirements for the success which he claims he has had. COUVY and his co-workers, LAMBERT, DUFOUR and POPOFF (1930 and 1932) report 21 severe cases of human plague with 15 recoveries and again, from a polyvalent phage, encouraging results with very little in the way of complications. A preliminary desensitization by the subcutaneous injection of the patient's own blood (autohaemotherapy) has been their routine practice to overcome the effect of anti-phage. COUVY (1932) has also insisted on a polyvalent phage in plague and that therapeutic action is a function of the lytic principle used. He affirms the perfect safety of treatment of plague by bacteriophage even by intravenous injection. Plague bacilli, which are abundant in gland juice obtained by puncture, are found to be in a state of lysis two hours after injection of phage. Some striking cases of bubonic plague have been cured in a few hours (COUVY 1932 b). " The curative action of an *appropriate* pestiphage is undoubted and rapid even in septicaemic plague." The findings of PONS (1932 b) for subcutaneous injection of pestiphage are very interesting : (1) Bacteriophage subcutaneously injected is rapidly generalized and produces in 24 hours a lysis of germs everywhere which, however, may not be complete. (2) In grave septicaemias injection of a lytic principle precipitates a toxaemia. (3) As long as lytic principle is demonstrable, cultures from either bubo or blood remain negative. (4) If during 48 hours the patient receives no bacteriophage, cultures from bubo or blood become positive, if the illness has a fatal issue, and remain negative in cases of recovery.

In the case of cholera in particular no one can afford to neglect the work and points raised by ASHESHOV (1930–32), which refer to the requirements of a therapeutic phage and to the pitfalls which beset the worker in this subject. Much of what is set out here is taken from the work of ASHESHOV.

Two characters of the bacteriophage are very liable to be confused: these are virulence and activity. Activity depends both on virulence and on the concentration of phage. Virulence is defined as an individual property independent of quantity and "can be estimated by the time in which a definite number of vibrios are destroyed by a definite number of phage corpuscles." The distinction is the usual one and applies to bacteria likewise. Virulence includes both a qualitative and a quantitative factor (BURNET, 1930a). The constant occurrence of phages of variable virulence is very important. ASHESHOV says:—"The existence of . . . races of bacteriophage of feeble virulence demands more attention in preparation of the bacteriophage cultures for practical application. It suggests the necessity of careful study of the race of bacteriophage used for that purpose. The use of 'raw' bacteriophages, isolated directly from, say, stools and mixing these direct filtrates without ascertaining the individual properties of each race used, may lead to undesirable results." Not only must we consider the potency of a phage from this point of view but also from the point of view of the bacterium. There are 'good' and 'bad' vibrios. Some vibrios when used for cultivation may yield a phage of higher virulence than do others, while some vibrios actually lead to diminution of virulence in the phage. Growth of bacteriophage on the wrong type of vibrio may bring about its denaturation. Vibrios after isolation alter very considerably and it is very essential that bacteriophage for therapeutic use should be grown on recently isolated vibrios. Grown on laboratory cultures, the bacteriophage may become, like the vibrio itself, denatured. The employment of an unsuitable phage may result in death of the phage instead of the bacterium or perhaps the establishment of symbiosis and a chronic disease. Such a chronic disease would require for its treatment a phage with virulence which exceeded that of the phage in symbiosis. Mention has been made also of anti-phage, due to the possession of antigenic properties by the phage. Such anti-phage in the blood may be a factor in the occurrence of slow cure, relapses and death (RAIGA, 1929). It was probably considerations such as these that prompted D'HERELLE to recommend the use in disease of an autobacteriophage. This, however, is scarcely possible in a rapidly fatal disease such as cholera. One of the methods recommended by ASHESHOV for keeping therapeutic phage virulent is to 'refresh' it by repeated cultivation on a freshly isolated vibrio." It is not always possible to obtain such vibrios and it takes time to determine their "goodness." Therefore a compromise may be made in the shape of cultivation of phage on the best laboratory strain available, described as ultrapure, that is not contaminated with phage, and as giving maximum virulence and maximum concentration of phage; such cultivation is to alternate with cultivation on freshly isolated strains.

As freshly isolated vibrios are so important for the upkeep of phage one may naturally ask whether it is essential to use freshly isolated phages for therapeutic purposes. MORISON (1932 b) in his recent annual report describes the procedure which he adopts in the preparation of therapeutic phage. It is that of an admixture of a large number of phages, constantly renewed. Fresh phages are obtained with certainty week by week and fresh bacteria are also procured. These are tested and at present 64 different combinations of bacteria and phage are being employed in each brew. This large number of combinations refers, however, to a phage intended for use in either cholera or dysentery. ASHESHOV, referring to the immediate

use of fresh recently isolated races of phage and their replacement as often as possible, admits that the procedure is theoretically logical and practicable, but condemns it, so far as cholera is concerned, as being neither in practice. He has not so far found a freshly isolated phage, particularly of the important A type, which satisfies the requirements already set out. Moreover, even if of equal virulence, such freshly isolated phages would be lacking in polyvirulence or in stability. His method is to pass the phages, which were nurtured in the laboratory and possessed greater virulence than those freshly isolated, through human beings with cholera and to reisolate them. Now, with the administration of phage in hospital to patients, it was not very long before everything in the hospital—utensils, linen, hands of attendants—was harbouring this bacteriophage, which easily contaminated the newcomer. The stools of patients who had been thus naturally infected with the therapeutic phage were collected, to be examined for virulence. "A part of the direct filtrate of the stools containing the best races was preserved in sealed ampoules for further use and a part was subcultured only once on the vibrio isolated from the patient. Only this first transfer was used for the production of bacteriophage for field use." Preservation of phage seems to have been effected by simply sealing in ampoules, in which it has been found by test to maintain its activity undiminished for some 11 months. The chief difficulty then for practical purposes is the procural of a suitable vibrio for propagation of phage and for the preparation of bacteriophage culture. The mixture which is now used by ASHESHOV "ABC IV" for prophylactic and curative treatment of cholera contains, as it must contain, all three phages A, B and C and lyses completely an emulsion of freshly isolated smooth vibrios in not more than two hours. The lysis is permanent in the majority of cases for at least 24 hours, very often for 72. Rough strains require 3 to 4 hours for their lysis. As phage is regarded as acting only in virtue of its being a living organism, no preservative may be added to therapeutic phage. This constitutes something of a difficulty in manufacture for storage. In the attempts so far made, especially with cholera phage A, to improve virulence and to obtain a more rapid lysis a limit appears to have been reached. It would seem then that as in the case of rabies virus a "fixed virus" state may have been attained. These details have been given fully as they require to be appreciated both for experimentation with phage and for its use in practice.

The details of original isolation of phage as a pure line strain, which may be regarded as derived from a single particle, also demand some attention. One method is given by BURNET (1930 a) :—"The centre of an isolated plaque is touched with a sterile needle and the trace of material so obtained is used to induce lysis in a young broth culture of the substrate bacterium. The procedure must be repeated once or twice to ensure that the phage is pure." Another method which is also used to obtain pure phage from a mixture is that of dilution to an extreme limit and the use of the highest dilution possessing activity as presumably pure. Neither method, however, excludes the possibility of the substrate bacterium being possessed of a latent lysogenic power, that is to say of being a bacterium in stable symbiosis with phage. For the separation of phage from bacterium it may be advisable to remember and, if necessary, to use the differential action of heat. Bacteria may be killed at a temperature

between 56 and 60°C., whereas "bacteriophage corpuscles are not destroyed until a temperature of 74 to 75°C. is reached."

As we began this section with the citation of instances of the use of phage, most of which were unsuccessful, we may fittingly now end it and this review by relating some of more favourable character. D'HERELLE considers that an epidemic comes to an end when the bacteriophage "contamination" becomes general. Not only so, but "experimentally we can choose a race of the most virulent bacteriophage already adapted to the rapid destruction of cholera vibrios. We can spread cultures of it over or at the very beginning of an epidemic more widely and more rapidly than is possible in the natural course of events" (D'HERELLE and MALONE 1927). It is therefore but a further step to apply these facts to prevention and treatment. In one village the epidemic of cholera came to an immediate end with the addition of 30 cc. of bacteriophage culture to the two wells supplying it with water (D'HERELLE and MALONE 1927). Most of the work in the prophylaxis and treatment of epidemic cholera has, as we have said, been done without statistically sufficient control. Such control is partially supplied in the trial, still under way, by MORISON (1932, a and b) in which two areas have been selected, one of which forms a control. In the test area bacteriophage has been supplied curatively for early cases of cholera, and by implication prophylactically for the expected following epidemic. The other area has been the control and has received no phage treatment. The results so far are all in favour of the area which has received phage. "The district has been free from cholera for a period twice as long as any during the last ten years." Five successive epidemic seasons have passed without an outbreak in the test area, while in the control area there has been an outbreak each season. The possibility, however, of a spontaneous decrease in cholera in the test area has evidently still to be reckoned with (MACKIE 1933). As an example of the therapeutic treatment of cholera, both in regard to results claimed and the detail of phage administration, we may take the account of ASHESHOV, KKAN and LAHIRI (1931) even though it is complicated by the simultaneous administration of hypertonic salt solution. That this treatment has roused the enthusiam of the authors to a very high pitch is evident and may be illustrated by their own statement that :—"We could hardly believe our own results. . . . The mortality from cholera . . . was reduced almost to nil . . . and when we say cholera we mean by it a severe attack of virulent Asiatic cholera." The bacteriophage was given undiluted in about drachm doses every 30 minutes. Two bottles, each containing 50 cc., should be finished by direct sipping in the first 16 hours. After the first 24 hours one bottle during the next 48 hours should generally suffice. For more rapid action bacteriophage may be given intravenously in 5 cc. doses, but must then be greatly diluted and is best administered with salt solution. A combined cholera and dysentery phage is likely to be useful (MORISON and VARDON, 1929) and is apparently already in use at the quarantine camp of El Tor (RUSSELL, 1932).

Commentary.

The frequency with which D'HERELLE has been quoted in this review, wherever important matters of theory and practice of bacteriophagy are involved, must not be taken as an indication of the measure of support which his views have obtained. It is true to say, however, that no satisfactory opposition has developed to those views. The

particulate character of the bacteriophage and its bacteriolytic action are accepted and its inclusion among the ultramicroscopic living viruses may be taken to be at least a reasonable deduction. That the bacteriophage, if it is an organism, is a single-species organism, on the other hand, is one of the most doubtful of D'HERELLE's arguments.

The cholera vibrio and the plague bacillus are two bacteria of very different action, the one an intestinal organism and the other essentially a septicaemic organism. Bacteriophage prophylaxis and therapy have made greater advances in cholera than in plague. Much of the work with both these diseases, however, is confusing, contradictory and uncontrolled, whilst failure of prophylactic or therapeutic action of the bacteriophage is apt to be accompanied by an apologia that is complicated and not convincing. We may hope that the trials in cholera at present progressing will afford the evidence of complete and permanent suppression of its epidemic character. None the less we are of opinion that proof of favourable action, unless dramatic and continued, is most likely to be obtained by the comparison of cases alternately treated with and without phage. In view of the conflicting opinions which are prevalent regarding the living virus-nature of the bacteriophage, the only judgment, which seems to us possible on this question, is one of non-proven.

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RECENT VIEWS UPON CLIMATIC BUBO AND SOME ALLIED CONDITIONS.

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Much light has been shed upon Climatic Bubo by the observations and experimental work of recent years, not so much upon climatic (or tropical) bubo itself, as upon what has proved to be the same disease as it occurs in temperate countries—Lymphogranuloma Inguinale.

When in 1913 Durand, Nicolas & Favre described L.I. in France, they were unaware of the disease known to every practitioner in the tropics, and at that time believed, as the name implies, that the affection L.I. was related to Hodgkin's disease. Attempts to demonstrate any causal organism failed and it was not until 1930, when Hellerström & Wassén showed that in the gland pulp and pus of the inguinal bubo an ultramicroscopic virus existed which could be passaged in monkeys by intracerebral inoculation, that the nature of the infection was established. The subsequent experimental work of Hellerström in Sweden, of Levaditi and his colleagues in Paris, of Marshall Findlay in London and others elsewhere, has now put us in possession of a considerable amount of knowledge concerning the virus and the tissue reactions which it excites in man and animals. Levaditi worked with strains obtained from French indigenous cases, Hellerström with mixed strains, while to Findlay we owe a comparative study of strains of virus obtained from cases of C.B. infected in the tropics with others derived from cases of L.I. whose infection was acquired in England. The published results obtained by these several workers have been reviewed in this *Bulletin* from time to time; they may be summarized as follows:—

The Virus.

C.B. and L.I. or as these two conditions may be called *Poradenitis tropica* and *Poradenitis nostras*, yield an identical virus. It is ultramicroscopic, filters through British Berkefeld filters, through Chamberland L_2 and with greater difficulty through L_3 candles. It is thrown down by ultra-centrifugation. In glycerine at low temperatures the virulence is preserved up to 10 days but lost at the end of 2 weeks. It is destroyed by heating to 60°C. for 30 minutes. It survives cooling to −2°C. or −3°C. for 10 days but is destroyed after 40 days, though it may be preserved dry in a frozen condition for 3 months. Drying *in vitro* over sulphuric acid at ordinary temperatures renders the virus inactive. Subjected to electrophoresis the virus like other ultra-microscopic viruses collects at the positive pole. The virus is present in the affected glands in man and in the sterile pus aspirated from a bubo. It may be transmitted to a number of experimental animals by suitable methods of inoculation.

Animal Experiments.

Many species of monkey are highly susceptible to intracerebral inoculation; after an incubation period of 4–8–22 days they develop symptoms of a meningo-encephalitis and show after death a characteristic pathological picture. The virus becomes generalized and can be demonstrated in the blood, liver, spleen, kidney and lymphatic

glands. Monkeys may also be successfully inoculated on the prepuce and in the groin with the production of a typical inguinal bubo. The virus reaches the glands before the primary lesion on the penis develops but does not become generalized under these conditions.

Mice form the most convenient animals for experimental infections. Intracerebral inoculation gives rise after a variable period of 5–34–94 days to a meningo-encephalitis similar to that in monkeys, with general dissemination of the virus. Intraperitoneal injection is followed by general dissemination but the animals do not die of a meningo-encephalitis unless the brain is traumatized at the same time. Local inoculations have failed to produce buboes in mice. The virus will not enter the unbroken skin of the mouse but infection follows scarification. In monkeys and mice passage by intracerebral inoculations of brain-emulsions may be kept up from animal to animal of the same species or from one species to another sometimes in long series; in other cases the virus tends to die out.

Guineapigs may be infected by groin inoculation with the formation of buboes and the infection passaged from animal to animal using groin-gland emulsions as the *inocula*. The virus may reach the mesenteric glands and occasionally the spleen, liver, kidney and lung but rarely the blood and never, as far as is known, the central nervous system. The virus may survive as long as 30 days in the brain of a guineapig after intracerebral inoculation but rarely are any changes produced. In the rabbit's brain similarly the virus may persist but no symptoms are produced. Groin inoculation in rabbits is unsuccessful. The rat is insusceptible. The dog and cat may be successfully infected by intracerebral inoculation and the infection passaged.

In the blood of animals which survive their infection there may be demonstrated the presence of substances which when mixed with active virus and injected into a susceptible animal render the virus inactive. The histopathological reactions in animals are similar to those occurring in man, they are very characteristic and have been well described among others by Marshall FINDLAY. In animal lesions the inclusion bodies described by GAMNA in human gland lesions and called after him, may be seen; they are referred to by FINDLAY.

LEVADITI and his co-workers have shown that the virus after animal passages, on preputial inoculation in man will excite the production of the typical inguinal bubo.

Frei's Reaction in Diagnosis.

Second only in importance to the experimental work on animals but preceding it by some years, was the demonstration by FREI in 1925 of the development of a specific skin allergy in cases of L.I. and of a method of testing for this using as antigen a suspension of pus or gland-pulp from an accepted typical case of L.I. Upon the precautions essential in preparing the antigen and the care necessary in evaluating the results of this intracuti-reaction FREI lays great stress in a series of articles already summarized in this *Bulletin*. Properly carried out FREI's skin reaction has proved to be a specific test of great value. L.I. antigens give positive reactions in cases of C.B. and conversely the skin of an L.I. patient reacts to an antigen prepared from a C.B.

With the two methods of investigation referred to above and a growing knowledge of the clinical side of the disease as more and more cases have come to be recognized in temperate countries, L.I.

has not only awakened much interest but assumed some importance in that a much wider view of this virus infection has been unfolded, and other conditions than inguinal poradenitis appear to be due to the same infection.

The Genito-ano-rectal Syndrome.

The first to receive attention (FREI, FREI & KOPPEL) was the affection known as chronic elephantiasis and ulceration of the vulva, a chronic disease of the female genitalia for which many aetiologies had been suggested including the other venereal diseases and tuberculosis. Other cases, in which there was also associated an affection of the rectum and anus, termed by JERSILD the genito-ano-rectal syndrome were next considered and then cases in which ano-rectal disease was found alone. The last mentioned affection is perhaps best referred to as chronic inflammatory stricture of the rectum; the stricture may appear as a single entity or form part of the whole syndrome. These conditions like elephantiasis vulvae have been variously thought to be due to syphilis, gonorrhoea, etc., in the past though the evidence when examined is almost entirely fallacious. On the other hand practically all the cases which have been collected and submitted to Frei's test using an L.I. antigen have yielded positive results. In only a few have attempts been made to recover the virus in animals but they have been successful. Reference to these conditions will be made again later.

Pathological Changes.

The histo-pathological picture, whatever the lesion, whether in man or experimental animal, may be said to be the same; variations are variations not in kind but in degree, according to the activity of the virus and the stage in the process. The changes consist in a reaction on the part of the lymphatic tissues to the pervading virus for which it has an exquisite predilection. The characteristic lesion consists in tiny pin-point epithelioid formations made up of cells of macrophage type together with some giant-cells; these microscopic nodes undergo central necrosis and then contain in their centres finely granular or amorphous material; later they are invaded by migratory cells which in turn degenerate with the formation of tiny stellate micro-abscesses, the forerunner of the multiple points of suppuration so characteristic of the inguinal adenitis. The normal tissues are entirely replaced by an inflammatory tissue consisting of young fibroblasts and a cellular infiltration remarkable for its polymorphism consisting of small lymphoid cells, medium-sized monocytes, fixed connective-tissue cells, young and adult plasma cells, large mononuclears from the reticulo-endothelium, basophil granulation cells and giant cells. In later stages a replacement fibrosis occurs. These changes are characteristic of the initial lesion, of the lymphangitis and the adenitis in C.B. and L.I. They are found in the hypertrophied tissues of genital elephantiasis in the male associated with poradenitis, in elephantiasis of the vulva, in inflammatory stricture of the rectum and other tissues involved in the complete genito-ano-rectal syndrome, BARTHELS & BIBERSTEIN having been responsible for some of the most interesting work on this part of the subject.

Historical.

The chapter on Climatic Bubo must be rewritten; lymphogranuloma inguinale as a clinical entity must perforce disappear; elephantiasis

vulvae and inflammatory stricture of the rectum must be rescued from the rubbish-heap of conditions of unknown aetiology. Together they must be considered as regional syndromes of a single infection, they constitute what for want of a better term at the moment I have referred to in a recent paper* upon the history of the recognition of these conditions, as a sixth venereal disease. In a monograph† published subsequently will be found a detailed review of the whole subject in all its aspects with a complete bibliography.

On the historical side little will be said here except to point out that what is probably the first description of C.B. was given by TROUSSEAU in 1865 referring to a condition among Creoles of Réunion and Maurice, and that the accounts given by a Dr. LIBERMAN, a surgeon in the French Expeditionary Force to Mexico as cited by BOURGET 1867, almost certainly have reference to the disease. In temperate countries what was afterwards called by DURAND, NICOLAS & FAVRE of Lyons lymphogranuloma inguinale had been well delineated long before, though commonly considered to be of syphilitic origin or strumous in nature. One of the best descriptions was given by William WALLACE of Dublin in 1833, others by KLOTZ of New York 1890, NÉLATON of Paris 1890 and MARION & GANDY 1901.

The attention drawn to the condition by the Lyons observers in 1913 led to the recognition of the disease in every country in Europe and in America but whereas on the continent the numbers of cases that have been reported had increased each year, no case of an indigenous infection with proof of the nature of the condition, had been recorded in this country until a case, which came under the observation of the writer in the autumn of 1932, was published.‡ Since then three cases have been recognized at the London Hospital, V.D. Clinic by Anwyl DAVIES and, in the opinion of the writer, as a knowledge of the condition spreads so will other cases be recognized in Great Britain. Inguinal poradenitis probably exists in every country in the world, though it is possible that it is localized rather to seaports and the larger cities.

Clinical Manifestations.

The contagion is usually communicated venereally but extragenital infections may occur, for example on the finger of the surgeon, and cases have been recorded in young children, including an infant 14 months old. The small papular, nodular or more commonly herpetiform primary lesion is most commonly situated in the male in the coronal sulcus but it is not so generally recognized that the initial sore may be within the urethra and give rise to an abacterial urethritis. A lymphangitis of the dorsal vessel of the penis is commoner than supposed.

Of the adenopathy little need be said here ; a single big abscess in place of multiple foci of suppuration may lead to difficulty in diagnosis unless realized. Very mild cases of adenitis may be missed unless laboratory tests are employed in diagnosis. Mixed infections must never be forgotten ; syphilis, chancroid, gonorrhoea and tuberculosis may complicate the case. The severity of the constitutional

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* *Proc. Roy. Soc. Med.* 1932. Nov. Vol 26. No. 1. pp. 7–15. (Sect. of Trop. Dis. & Parasit., pp. 1–9.)

† STANNUS, H. S. A Sixth Venereal Disease. 1933. [Now in the press for publication by Baillière, Tindall & Cox, London.]

‡ STANNUS, H. S. & FINDLAY, G. Marshall, *Lancet.* 18/2/1933. p. 358.

symptoms may be misleading. They occur generally in the earlier stages; nausea, vomiting, rigors and sweats may be marked features; a pulmonary reaction in the form of bronchitis and a meningeal reaction with intense headache and stiffness of the neck have been recorded. Prolonged pyrexia may occur and a typhoidal state supervene. The enlargement of the intra-abdominal glands may be so great as to give rise to pressure symptoms. Splenic enlargement and a generalized adenopathy have been described. Rheumatic pains and arthritis are not uncommon and associated sometimes with episcleritis. Erythema nodosum and E. multiforme are also seen.

At one time C.B. was considered a disease restricted to the male sex, and it was not till it was realized that the typical inguinal bubo occurred in cases of L.I. in women that this fallacy was corrected. In women if the initial lesion be sited on the vulva, whence the lymph flow is towards the inguinal glands, then an inguinal bubo results as in the male. It has been suggested that the gland reaction may be minimal with persisting infection about the female genitalia. Probably in the majority of cases of infection in the female the primary lesion occurs in the posterior part of the vulva or most commonly within the vagina on the posterior wall, in the lower third. Under these circumstances though some part of the infected lymph-stream may reach the inguinal glands the brunt of the infection falls upon intra-pelvic glands, in them setting up changes similar to those seen in the glands and periglandular connective tissue of the groin. The course of such an infection as well as the results may be varied. The glands which are attacked appear to be those lying in the recto-vaginal septum, the ano-rectal or para-rectal glands. In some cases suppuration appears to be minimal and fistulae do not develop or form a minor part of the condition; periadenitis and infiltration of the connective tissues are marked and can be felt about the vagina and rectum; a plastic inflammation of the parametrium may fix the uterus and the adnexa may be involved. In other cases the lymph-glands undergo softening, fistulae develop which open into the vagina, the rectum or on the skin surface about the anus. The disease as in infections elsewhere may come to a natural end or the infection may persist over a very long period with the production of much more serious conditions even though the activity of the virus has become much diminished. In these chronic cases infection may spread to successive groups of pelvic glands with the production of extensive lymph-blocking. It also spreads by a retrograde lymphangitis into the connective tissues and organs whose lymph drains to these glands. The resulting conditions are therefore not merely caused by lymph stasis but are due to a specific inflammatory reaction on the part of the tissues to the virus. This has been very beautifully demonstrated by the pathological work of Barthels & Biberstein. Thus are produced those several conditions included under the term genito-ano-rectal syndrome, or Esthiomène, the name invented by Huguier who gave the first systematic description of the affection in 1848 though the first record I have been able to discover was by Desruelles four years earlier.

When the process is limited to the pararectal tissues, inflammatory stricture of the rectum may be the outstanding effect; in the same way the incidence may chiefly fall upon the vulva with the production of elephantiasis of the vulva; or the whole genito-ano-rectal syndrome may appear.

This part of the subject is a large one and has been very fully discussed in the monograph mentioned above; it will only be possible to make a short reference to it here. This particular type of stricture is characterized by: female sex preponderance, long history, position 2 to 6 cm. above the anus, *i.e.*, in the ampulla, most commonly at 2 or 6 cm., where the lymph plexus is best developed; the stenosis is caused by infiltration from without and not from within, the mucous membrane covering the stricture is intact and not the seat of scar tissue, but ulceration may be found below the stricture, fistulae are often present below the stricture, a polypose condition of the mucous membrane is often seen above the anus and in the region of the anus condyloma-like growths may exist, together with an elephantoid condition of the skin in the neighbourhood. The condition is really one analogous to the elephantiasis of the vulva. The process affecting the vulva may be diffuse or limited to some one part. Hypertrophy and ulceration may co-exist or either may be the more marked feature. In extreme cases with hypertrophy the labia or nymphae and preputium clitoridis may form tumours the size of coconuts covered with papillated or polypose elephantoid skin. In extreme cases when ulceration predominates, destruction of tissue may go on to the formation of a cloaca into which the remains of the urethra, vagina and rectum open.

A review of all the published cases of Esthiomène will be found in the monograph above referred to; the condition has been described in every country in Europe and in America. The first case in Great Britain was by McClintock (1863) and others were noted by the English gynaecologists West and Barnes. There are, so far as I have been able to discover, very few references to the conditions included under the genito-ano-rectal syndrome from tropical countries, where indeed we might expect to find them more commonly than in temperate countries. The reason lies in the fact, I believe, that for the most part they occur among natives of the prostitute class of low degree who hide their ills and, when seen, they are relegated to the category of syphilitic manifestations, and not recorded.

Branfoot (1902) unquestionably saw cases of esthiomène in India but confused them with granuloma venereum. I have myself seen typical cases of esthiomène in Central Africa. Boerma and later Roegholt (1926) wrote upon a rectal condition among natives of the Dutch East Indies which surely belonged to our group, and Joachimovits (1929) has given excellent accounts of the genito-ano-rectal syndrome as seen in Javanese prostitutes, though he did not recognize the cause and thought that chancroid infections played a part in causation. Inflammatory stricture of the rectum alone is probably not uncommon among certain native races. Surgeons practising in India have referred to "syphilitic" strictures as being common but it seems doubtful if they were syphilitic. Jeffreys & Maxwell speak of non-malignant rectal strictures as common among the Chinese. They have been noted among natives in various parts of Africa, are frequently observed in Cuba and well known among negroes in the United States. All the conditions included under the term genito-ano-rectal syndrome have, I believe, a world-wide distribution, though the number of cases, as in poradenitis, may be comparatively small.

There are many wide gaps in our knowledge of climatic bubo and those other conditions believed to be due to the same virus infection.

Further observations and records upon these affections in tropical countries are urgently needed, more especially if they can be controlled and confirmed by laboratory methods. Published and unpublished observations sent to the Bureau of Hygiene and Tropical Diseases would be welcomed.

SLEEPING SICKNESS.

LESTER (H. M. O.). **Sleeping Sickness in Northern Nigeria. A Review of Events Leading to the Adoption of Present Methods.**—*West African Med. Jl.* 1933. Jan. Vol. 6. No. 3. pp. 50–53. [12 refs.]

This paper describes the history of sleeping sickness work in Northern Nigeria, where the problems are rather different from those in other parts of Africa, owing to the fact that the country is ruled through its own Emirs and Chiefs.

During the last few years there has been a big increase in the number of cases of sleeping sickness treated in the Northern Provinces, but there can be no question that there has been a disconcerting spread of human trypanosomiasis into areas which were previously little affected. The author believes that the causes of this are due to the changes following British occupation. Previously the people tended to collect for protection into large walled towns and limited their farming to the immediate vicinity of these towns, which consequently were protected from tsetse by the large clearings around them. Following the occupation the people spread all over the country and the general population is much more exposed to fly than formerly. Similarly, the progressive settlement of the country has led to greater facilities for trade and travel. As there is no province in Nigeria free from tsetse it is clear that increased travelling has caused the disease to spread to areas previously free from sleeping sickness.

There follows a brief history of sleeping sickness in Northern Nigeria up to 1921, when JOHNSON and LLOYD were appointed to investigate the tsetse fly problem in Northern Nigeria. From this date onwards there has been a progressive increase in the number of cases treated. In 1926 some 298 cases were treated mainly with tryparsamide. In 1927, 364 cases were treated at Sherifuri and 82 at other stations. Towards the end of this year four sleeping sickness officers started work, and in 1928 they treated no less than 3,012 cases, whilst 82 cases were treated by the rest of the medical staff. As the result of JOHNSON's journey across Africa to observe methods of trypanosomiasis control in various Belgian, French and British Dependencies, he recommended that there should be a re-organization of the Tsetse Investigation Staff, and that provision should be made for the compulsory treatment of natives where necessary. These recommendations could not be put into practice before 1930. In 1929, the sleeping sickness staff treated 3,629 cases. Although this was a big improvement matters were still far from satisfactory, because the majority of patients received only 2 or 3 injections of tryparsamide and soon relapsed. It was then decided that every effort must be made to persuade patients to attend for a full course of treatment. In 1930, 3,377 cases were treated and a fair proportion of these received a full course of tryparsamide. In addition, a further 1,857 cases were treated by the general medical staff.

The author then passes to a consideration of the French method of sleeping sickness control and the possibility of the application of the French methods to Nigeria. The Nigerian system of indirect rule made it necessary for these methods to be modified before they could be applied in Nigeria. In the French Colonies the sleeping sickness team was accompanied by a force of Native Police, who used direct

measures to enforce the attendance of the whole population for examination and treatment. This cannot be done in Nigeria, and it is obvious that here the one hope of success lies in the active co-operation and support of the Native Administrations. In a later paper it is hoped to give a detailed description of the methods which had been adopted in carrying out a mass examination in a Hausa Emirate.

For the greater part of 1931 it was only possible to have one team at work in the field, but towards the end of the year a second team was appointed. Up to September, 1932, these teams have treated about 10,000 cases. *W. Yorke.*

LESTER (H. M. O.). **Report of the Tsetse Investigation.**—*Nigeria Rep. on the Med. & Health Dept. for Year 1931.* Appendix B. pp. 89–98.

The first part of this report deals with laboratory work carried out at Gadau.

The work on the nature of certain trypanosome strains isolated from sleeping sickness patients has been continued. The Gadau strains 1 to 5 are comparatively avirulent in laboratory animals, whereas strain Ayu 6, the local strain 6 and an old London strain were all very virulent. Strain Ayu 6 is completely resistant to tryparsamide, while two others, viz., Gadau 1 and 6, exhibited a considerable degree of resistance to this drug.

The author writes that it seems to be very significant that 3 of 10 strains tested show a natural resistance to tryparsamide in small laboratory animals. Strain Gadau 4, which was originally very sensitive to tryparsamide, was made arsenic-fast ; it was not possible to discover whether this acquired character could be transmitted by the fly, because all attempts at transmission failed, probably because the strain had become non-transmissible during the necessary manipulation. On the other hand, strain Ayu 6 was found to be tryparsamide-resistant after passage through *G. morsitans*, though in this case it is probable that the arsenic-resistance is a natural as opposed to an acquired character.

In vitro tests were carried out with all these strains. It was found, whereas Gadau strains 1 to 5 and Ayu 5 were all completely insensitive to human serum, strains Ayu 6, Gadau 6 and the London strain were all killed in under 3 hours. The author concludes that the strains Ayu 6 and Gadau 6 had many of the characteristics usually ascribed to *T. rhodesiense*, while Gadau 2, 4, 5, and Ayu 5 resembled the classical *T. gambiense*. Three strains Gadau 1, 3, and Ayu 5 (*sic*) had intermediate characters.

Cerebrospinal fluids from sleeping sickness patients were examined by the bi-coloured guaiac test and the findings controlled by a white cell count. The curves were of the flat or plateau type very similar to that found in general paralysis.

Work on the transmissibility of *T. gambiense* strains by *G. tachinoides* has been continued. DUKE's findings in East Africa have not been confirmed for these Nigerian strains, as, when reasonably large numbers of flies were employed, all the strains examined proved to be cyclically transmissible by tsetse.

The next part of the report deals with the field work. The results so far obtained on " trapping " have not been encouraging. During

the year some 5,000 cases of sleeping sickness have been treated and practically all cases have been given a full course of 20 to 30 gm. tryparsamide.

Details are given of the work of the sleeping sickness staff and information is supplied concerning the districts found to be infected.

The last section of the report deals with the treatment of sleeping sickness cases in the Jemaa and Jos Divisions.

Interesting information is given regarding the re-examination of sleeping sickness patients in Ayu District. Out of a total of 172 cases diagnosed in April, 1931, there were 7 deaths, leaving 165 who attended for treatment. Treatment with tryparsamide (24 gm. per adult) was given in June and July. In November, 155 were re-examined for enlarged glands and the presence of *T. gambiense* in the gland juice and blood. The great majority showed either no glands or small firm glands as the result of treatment. The spinal fluid was re-examined in 84, a large number of cases with original normal cell counts not having their cerebrospinal fluid re-examined. The results are given in the following table :—

Groups.	Treatment.	Original cell count.	White cell count in C.S.F. after Treatment.					Total cases.
			Normal.	Reduced.		Unchanged.	Increased.	
				Greatly.	Slightly.			
1	Full course	Increased	26	10	5	5	1	47
2	Full course	Normal	7	...	...	...	...	7
3	2 inj. ...	Increased	15	1	...	1	1	18
4	2 inj. ...	Normal	7	...	...	...	2	9
5	Nil ...	Increased	...	...	...	...	2	2
6	Nil ...	Normal	1	...	...	...	...	1
								84

The author remarks that the greatest interest attaches to Group 3, who had only two injections of tryparsamide, and who originally had increased cell counts ; 15 out of the 18 were apparently cured by this small amount. *W. Y.*

ZSCHUCKE (Johannes). Beitrag zur Kenntnis der Schlafkrankheit in den westafrikanischen Küstengebieten. [**Sleeping Sickness in the West Africa Coastal Region.**]—*Ztschr. f. Hyg. u. Infektionskr.* 1932. Nov. 29. Vol. 114. No. 3. pp. 464–500. With 7 charts. [61 refs.]

The author states that he went to Spanish Guinea in 1928 with two main objects in view : firstly to compare sleeping sickness in West Africa with that found in East Africa, and secondly to subject to a systematic test certain new trypanocidal remedies and to contrast their action with that of other well-known drugs.

The first portion of the paper relates to general manifestations of the disease. He reached the conclusion that the so-called trypanosomal chancre is probably always present in European cases of sleeping sickness contracted in West Africa, but that it is never seen in native cases either in West or East Africa.

In West Africa the disease in the European is characterized by an intermittent fever which runs an irregular course; this is seen in East African natives and often in natives of the Cameroons, but rarely in the Coast natives at Fernando Po. In a table the author summarizes the signs exhibited by 218 cases (104 early and 114 late) of sleeping sickness in West African Coastal natives. The frequency of clinically latent cases of sleeping sickness amongst Coastal natives appears to be associated with the scantiness of the trypanosomes in the blood, lymph glands and spinal fluid.

In view of the fact that there are often very few clinical symptoms and that search for the parasite is often in vain, the questions of diagnosis and therapy are frequently matters of difficulty. The author consequently devoted much attention to discussing the various haematological, serological, and other aids to diagnosis.

The following summary is given :—

Trypanosomiasis of the West African Coastal native is to be distinguished from that of East Africa and especially from that of Europeans by the absence of the trypanosomal chancre, by the rareness of skin and general signs, and by the paucity of parasites in the blood, lymph glands, and cerebrospinal fluid. Among the nervous symptoms, the spinal manifestations outweigh the cerebral, and among the psychical anomalies, psychomotor inhibition is more pronounced than is psychomotor excitation.

These observations are considered to be an expression of a change in the character of the disease, not so much because the virus has possibly become attenuated in the course of a century, but because the West African people, thanks to natural selection, have gradually become resistant to the trypanosome and because this resistance has inhibited the generalization of the virus and the allergic re-tuning of the whole organism.

On this hypothesis there arises a new viewpoint for therapy and explanations of the divergencies of opinion regarding the most important of the therapeutic agents hitherto discovered.

Consideration of the various laboratory methods for the diagnosis, prognosis, and therapy of sleeping sickness has shown that haematological and serological methods are generally of little value, but that examination of the cerebro-spinal fluid, especially by colloido-chemical methods, is very useful. *W. Y.*

UGANDA PROTECTORATE. **Annual Report of the Human Trypanosomiasis Research Institute for the Year ended 31st December, 1932** [DUKE (H. Lyndhurst), Director].—10 pp. 1933. Entebbe: Govt. Printer. [Sh. 1.]

Owing to the fact that the Human Trypanosomiasis Research Institute at Entebbe no longer receives financial support from the other East African Colonies, its income during 1932 was reduced from £9,000 to £4,500 per annum. This has necessitated the reduction of the European staff to a Director, Bacteriologist and Laboratory Assistant. Late in January, 1932, the old laboratory was vacated and possession was taken of the new laboratory building. Owing to the lack of funds half this building at present stands idle, devoid of all internal fittings, and the floors, walls and ceiling unfinished. A brief description of the new laboratory is given.

During the year 4 safaris were undertaken. In May Dr. WALLACE visited the *morsitans* belt of Mbarara, and later the *pallidipes* area on the Busoga coast line; DUKE himself visited Damba Island in February, and in August he went to the Ngussi River.

In August some alarm was occasioned by the discovery near Kampala of several cases of a very acute form of human trypanosomiasis, the

sufferers being in one or two cases picked up comatose by the roadside. The trypanosome concerned was found to be *T. rhodesiense.* The patients came from the Buzinza country over the Tanganyika border, where human trypanosomiasis was unknown until the appearance of these cases in Uganda. Measures have now been begun to check the introduction into Uganda of this highly undesirable trypanosome. In Duke's opinion the danger was very real, as *G. morsitans* is found along Uganda's south-west frontier, and miles of *palpalis* shoreline lie open to invasion on the Sesse Islands and the adjacent mainland. It is noted that the strains from these Buzinza cases are found to be readily transmissible by *G. palpalis* in the laboratory.

The remainder of the report is concerned with summarizing the scientific work done at the laboratory during the year. This has for the most part already been published and noticed in this *Bulletin.*

W. Y.

KELLERSBERGER (E. R.). **African Sleeping Sickness. A Review of 9,000 Cases from a Central African Clinic.**—*Amer. Jl. Trop. Med.* 1933. Mar. Vol. 13. No. 2. pp. 211–236. With 15 figs. [21 refs.]

This article gives a very interesting account of the author's work on sleeping sickness, its symptomatology and treatment at the Bibanga Mission in the Katanga Province of the Belgian Congo.

A hospital with about 200 beds was completed in 1923. Between this date and 1932 approximately 30,000 patients have been registered, and of these about 9,000 were suffering from trypanosomiasis. All were of the *T. gambiense* type and were infected by *G. palpalis.* As far as possible all cases were followed up for two years or more after treatment, and considering the primitive nature of the people a remarkably large proportion (75 per cent.) has been observed over a long time. Over 400 died in hospital, death being due either directly to advanced disease or to an inability to take drugs, but more often from complicating diseases. A small percentage was lost sight of and another small group did not finish treatment; undoubtedly many of these died. The mortality was much increased by the fact that many cases were brought to the hospital far advanced, often after having been abandoned by their people.

In most cases diagnosis was made by blood smear, gland puncture, or lumbar puncture. Only in advanced cases was it difficult to find the parasite, and here clincial symptoms were usually so pronounced that diagnosis was simple. The patients were classified into three categories.

The first consisted of those in good health with trypanosomes in the blood stream. Very early cases were rarely encountered, as very few natives reported for examination at this stage and the infection was only discovered accidentally. The author writes that symptoms do not appear for several weeks after infection. Some months later, the lymphatic glands become enlarged. The patients belonging to this group mostly presented themselves because of attacks of remittent fever, or chronic headaches, or general ill health.

The second group includes those who showed definite clinical symptoms—swollen glands in the neck, constant headaches, or irregular fevers; others complained of sexual impotence, or miscarriage, or sterility. There is often the telltale expression, " a certain intangible,

swollen, stupid look that one finds only in this disease." Nervous symptoms, such as tremors, slurred speech, mental dullness, also appear. In this group trypanosomes were seldom found in the blood, but were almost always discovered by gland puncture. This group represents the largest number and contains about 75 per cent. of the author's cases.

The third group is really an advanced second group. It is the most discouraging and difficult of all. Many die in their villages, ostracized or abandoned by their people. They spend hours in stuporous sleep, or are driven into the forest by their mania, to perish miserably from hunger or exposure, or to fall victims to a wild beast, or to an army of driver ants. A very graphic description is given of the symptoms and signs exhibited by this group of patients.

Four drugs were used by the author, viz., atoxyl, antimony, Bayer 205, and tryparsamide. He agrees with CORSON and others that in early cases Bayer 205 is the best drug, but, unfortunately, most cases do not come early enough. He is convinced that with *T. gambiense* infections, all later cases, i.e., with central nervous system involvement, finally relapse after Bayer 205. Undoubtedly the most useful drug for his work was tryparsamide, and since 1925 this drug has been given to nearly 8,000 cases. The routine procedure is now a series of weekly injections, each dose being 0·045 gm. per kilo. of body weight.

The author further considers that in all cases where the central nervous system is involved, a second course should be given after a rest period varying from 1 to 3 months, according to the condition of the patient. Experience shows that the drug can be continued over long periods and as much as 100 gm. have been given in a course. When in doubt a second course is given, though many cases are cured by only one series of injections.

At the end of this very interesting report details are given regarding nine cases treated with tryparsamide. Some of these cases were apparently cured by a single course of the drug, whilst two of them, viz., Case 712 and Case 116, received two or three courses. Unfortunately, from the data supplied, it is by no means certain that Case 712 was not cured by the first course, and Case 116 by the second if not the first. Case 712 is particularly interesting. Before treatment in August, 1926, lumbar puncture showed 1,800 cells, and the patient was unbalanced mentally. After 8 injections totalling 20 gm. of tryparsamide, lumbar puncture showed only 48 cells; three months later a second course of injections was given, and subsequent lumbar puncture showed 24 cells. A year later, without any further treatment, lumbar puncture showed 10 cells, and two years later than this, again without treatment, lumbar puncture showed two cells; three years later the patient was still in excellent health.

[It seems to the reviewer very doubtful whether the patient was not cured by the first course, and that the spinal fluid might well have become normal without a second course. The point is of importance. It is frequently stated in the literature that a number of courses of tryparsamide are often necessary to effect a cure, but the evidence that this is a fact is usually most unsatisfactory. In the reviewer's experience with experimentally infected rabbits if the first course fails to effect a cure further courses are useless. The reason for this is perfectly clear; rabbits which are not cured by the first course develop resistant strains of trypanosomes.] *W. Y.*

DYLEFF (P.). Quelques réflexions sur la disparition spontanée des trypanosomes chez trois européens reconnus porteurs des trypanosomes. [**Spontaneous Disappearance of Trypanosomes from Three Europeans.**]—*Bull. Soc. Path. Exot.* 1932. Nov. 9. Vol. 25. No. 9. pp. 956–958.

Details are given of three Europeans in whom trypanosomes were found and whose blood subsequently became negative without treatment and remained so for prolonged periods.

The blood of four Europeans was examined for trypanosomes, by the triple centrifugation method, at the Consortium Minier Congo Niari, Mindouli, on the 15th February 1932. In two of the four trypanosomes were found. The patients, who showed no signs of the disease, were sent to Brazzaville—a 4 or 5 hours' journey by motor car. They were examined at Brazzaville immediately after their arrival with negative results. A week later they were again examined with negative results. One of the patients was then sent to France and examined by MESNIL, again without success; the other elected to remain under observation at Brazzaville and 9 or 10 blood examinations (triple-centrifuge) have all been negative.

The details of a third case discovered in the same locality 29th February 1932, are very similar. *W. Y.*

ECONOMIC ADVISORY COUNCIL. **Tsetse Fly Committee Report. Developments in the Treatment of Animal and Human Trypanosomiasis and in Tsetse Fly Control in the Period 1925–31** [PLYMOUTH, Chairman].—27 pp. 1933. London: H.M.S.O. [6d.]

The Tsetse Fly Committee was appointed in 1925 and naturally its first duty was to consider a plan of procedure for a campaign to control the conveyer of trypanosomiasis. In October of that year their first report was presented to the Committee of Civil Research (now the Economic Advisory Council), putting forward certain recommendations as to what ought to be undertaken in each of the East and West African territories. They expressed the view that local control was primarily the function of local administrations and that the cost of such should fall on the respective Governments, but that research should be under the direction of a Permanent Trypanosomiasis Committee. The latter recommendation not meeting with general acceptance, it was decided that the Tsetse Fly Committee should carry out the functions of the proposed Trypanosomiasis Committee, but in an advisory capacity only.

The report proper on the six years' work, 1925–31, is divided into four sections:—

1. *Developments in the Treatment of Animal Trypanosomiasis*, with subsections on the species of trypanosome present (*T. brucei* causing nagana in horses and dogs, *T. congolense* and the less virulent *T. vivax* infecting cattle), variations in course of the disease (depending on the number of infecting flies, the species of parasite in relation to the host, and the important question of latent or dormant infection, immunity-tolerance or premunition), the methods of diagnosis (as by provocative injection of halarsine, or of antimosan, by animal inoculation, complement fixation and the adhesion phenomenon, of which the penultimate would seem to be the best), on chemotherapy (especially with naganol and certain antimony compounds) and on

measures of control (as by genetic means—suitable crossing with immune native cattle—by isolation, by dipping, by chemical prophylaxis and attempts at immunization).

2. *Developments in the treatment of human trypanosomiasis*, by Bayer 205 and Tryparsamide, separately and in combination, for cure or prophylaxis [the tests with the styryl compounds are not referred to].

3. *Development of measures for control of tsetse flies*, by reclamation, by grass fires, strip-clearings, game and fly barriers (planting broad strips of dense thicket in which cattle tsetses as *G. morsitans* and *G. swynnertoni* cannot live), by catching of flies by hand or trap. This section ends with a brief sketch of the results attained in Shinyanga and Mwanza (Tanganyika), in Sherifuri and Matyoro lakes region (Nigeria).

Lastly is a short section giving the Committee's conclusions as to the results obtained in each of the three fields dealt with in the preceding sections.

The whole subject, especially regarded from the scientific aspects, was considered in much greater detail in the publications on Medical Research in the Colonies, Protectorates and Mandated Territories, issued by the Colonial Medical Research Committee (which was dissolved in 1930) in 1928, 1929 and 1930. In these were discussed for each Colony in turn, the situation at the time, the researches in progress, the measures attempted or adopted and the results. These publications were issued for official distribution and several copies were sent to each Colony and to each worker in this field who was thus made acquainted with progress elsewhere also.

In the space here available these details cannot be adequately given, but the general situation may be gathered from the concluding observations of the Committee from which the following is taken :—

" (*a*) Treatment of animal trypanosomiasis.

" The period under review has been marked by progress in the recognition of the nature and complexity of the problem presented by animal trypanosomiasis, and this has been accompanied by a considerable advance in regard to the fundamental question of diagnosis. Of special importance has been the recognition of the part played by latent trypanosomiasis in increasing the losses connected with rinderpest immunisation, especially in West Africa, and the successful application of measures to eliminate or minimise this factor. Drug treatment has also made considerable progress. In the camel trypanosomiasis of the Sudan, improved methods both of diagnosis and treatment have now made it possible for the disease to be attacked with a very considerable degree of confidence. In the trypanosomiasis of cattle, the action of antimony compounds has been further studied and methods of administration improved and standardized. . . . This treatment . . . is rendering . . . possible agricultural and mining developments that otherwise could be carried through only with great difficulty. The success that has been attained has, however, emphasised the need for the prosecution of further research on the widest practicable scale.

" (*b*) Treatment of human trypanosomiasis.

" Work on human trypanosomiasis in recent years shows that germanin (Bayer 205) if given in the early stage of infection by *T. gambiense* is curative, but that in *T. rhodesiense* infection, the results are less certain. . . . The present tendency in British territories in Africa is to give first germanin and later a course of tryparsamide, and this is probably the best form of treatment in cases in which it is impracticable to ascertain the

state of the spinal fluid by lumbar puncture. The value of germanin for the prevention of sleeping sickness in a native community is not yet satisfactorily established.

" (*c*) Tsetse fly control.

" The Report shows clearly how serious is the tsetse fly menace in many parts of Africa. Over large stretches of territory no economic progress will be possible until this problem has been successfully tackled, and even in areas that are at present settled there is often a danger that an advance of fly may take a heavy toll both of human life and of the livestock on which the native largely depends for his existence. In extreme cases there may in present conditions be no alternative to the evacuation of the population and the surrender of territory to the fly.

" Research for improved methods of tsetse control, far from being of academic or scientific interest only, is thus a problem of great urgency and practical importance to many of the colonial administrations in Africa."

" The most important work has been that carried out under Mr. Swynnerton's directions by the Tsetse Research Department of the Tanganyika Territory. This has brought within measurable distance the practical solution of many aspects of the tsetse problem. It is thus in the truest sense of the term pioneer work of the utmost value to every country where tsetse flies occur. The Committee trust that, notwithstanding the present financial stringency, every effort will be made in this and following years to provide the funds necessary for the continuance of this work, the successful conclusion of which is vital not only to Tanganyika, some two-thirds of the area of which is under fly, but also to other fly-infested territories in Africa. . . ." *H. H. S.*

DUKE (H. Lyndhurst). **Studies on the Factors that may influence the Transmission of the Polymorphic Trypanosomes by Tsetse. I. A Review of Existing Knowledge on this Subject, with Some General Observations. II. On the Transmitting Power of Different Races of** *Glossina*. **III.** *Glossina morsitans* **versus** *Glossina palpalis* **as a Transmitter of the Polymorphic Group of Trypanosomes.**—*Ann. Trop. Med. & Parasit.* 1933. Apr. 10. Vol. 27. No. 1. pp. 99–118. [19 refs.]; 119–121; 123–130.

A study of the factors which influence the transmission of the polymorphic trypanosomes by tsetse and firstly of the transmitting power of different races of fly and a comparison of the transmitting power of *palpalis* and *morsitans*.

The author summarizes his first paper as follows:

" 1. A consideration of the results of the dissection of wild tsetse by a number of observers in different parts of Africa suggests that the adjustment between the mammalian trypanosomes and the tsetse upon which they depend in nature is not very close. Of the pathogenic mammalian trypanosomes, the proboscis-only group, comprising *T. vivax* and its allies, is almost always the most widely distributed in wild tsetse, and the polymorphic group is the least successful.

" 2. In theory, transmission experiments with laboratory-bred tsetse should yield a higher infection rate than that obtaining in wild flies. Table II shows that the carrying power of the tsetse, under what appear to be abnormally favourable conditions, rarely exceeds 20 per cent. when an adequate sample of flies is taken.

" 3. There are indications that the full carrying capacity of a given tsetse population in nature may often remain untested owing to the prevalence in the area of food animals that are unsuitable hosts for the trypanosomes that depend upon the tsetse. Baboons and large reptiles, possibly elephants and probably hippo and wild pig fall into this category of food animals.

"4. There are indications that only a certain limited number of individuals of any tsetse population are able to act as hosts for trypanosomes. The existence of double infections of the same fly with two different species of trypanosome supports this conclusion. These gifted individuals appear to constitute but a small proportion of a fly population and to be suited to all species of trypanosomes that can develop in tsetse, whether mammalian or reptilian. It is probable that species and also strains of trypanosomes differ in their ability to utilise these potential carriers.

"5. The indications in favour of climate being an important factor in determining the infection rate are not at all clear. More experimental and field work is required on this subject.

"6. There are indications that *G. pallidipes* may in certain circumstances attain a relatively high standard of efficiency as a carrier of the pathogenic mammalian trypanosomes. Whether this is determined by climate, or by the racial peculiarities or the feeding proclivities of this fly, cannot yet be determined.

"7. Unilateral infections of the salivary glands have been shown to occur in both *G. morsitans* and *G. palpalis* in flies dissected during laboratory transmission experiments.

"8. It has been shown that *G. morsitans* in nature may be infected with a trypanosome of the *T. grayi* type, an observation which strongly suggests that this species of tsetse on occasion feeds on reptiles in nature."

II. This paper relates to an experiment devised with the object of ascertaining whether different races of tsetse from different localities differ appreciably in their susceptibility to infection with trypanosomes. *G. palpalis* were obtained from two sources, viz.—(1) Mainland flies at Nakiaga, and (2) Damba flies. Pairs of boxes, each box containing some 50 flies from one of the two localities, were fed twice, with a day's starvation between the feeds, on a monkey carrying a trypanosome known to be transmissible by *palpalis*. *T. gambiense* and *T. rhodesiense* were the trypanosomes used. The results of the experiment are summarized in a table, and show very striking agreement between the two groups of flies.

III. In this interesting paper the author has investigated the question whether the transmitting power of *G. morsitans* and *G. palpalis* is the same. He summarizes his results as follows:—

"1. Evidence has been produced to show that *G. morsitans* is a more efficient vector of the trypanosomes of the polymorphic group than is *G. palpalis*.

"2. Of a total of 3,119 *G. morsitans*, 203 (6·5 per cent.) were found on dissection to contain flagellates. Of a total of 3,236 *G. palpalis* treated in exactly the same manner, 95 (2·9 per cent.) contained flagellates. Of these grand totals, 881 flies of each species belonged to the experiments of Kleine and Fischer.

"3. Although the carrying power of *G. morsitans*, as revealed by these experiments, appears to be almost twice as great as that of *G. palpalis*, even the former species, in the conditions of experiment prevailing at Entebbe, is but poorly adjusted to the requirements of the polymorphic group.

"4. A strain of *T. gambiense*, judged to be non-transmissible by *G. palpalis* as the result of testing with several thousand flies, when tested by *G. morsitans* proved also non-transmissible by this species." *W. Y.*

CORSON (J. F.). **A Note on Some Experiments on the Action** *in vitro* **of Normal Human Serum on** *Trypanosoma brucei* and *T. rhodesiense*.—*Jl. Trop. Med. & Hyg.* 1933. Feb. 15. Vol. 36. No. 4. pp. 53–55.

This paper records experiments bearing on the question whether trypanocidal activity *in vitro* of serum is connected with the animal's

resistance to infection. Three strains of trypanosomes were used, viz., a strain of *T. brucei* from Natal, a strain of *T. brucei* from Tanganyika, and a strain of *T. rhodesiense* also from Tanganyika.

The Natal strain of *T. brucei* infected only about half the rats inoculated at one time and failed to infect guineapigs; it also failed to infect four European volunteers. The Tanganyika *T. brucei* never failed to infect rats, but guineapigs were resistant, although not quite immune. The *T. rhodesiense* strain was obtained by injecting rats with the cerebrospinal fluid from a human being; and of the two rats inoculated, only one became infected.

The object of the experiments was to ascertain whether guineapig serum had any trypanocidal action on the Tanganyika *T. brucei*; if the serum of a rat which had previously resisted infection with *T. brucei* in Natal was trypanocidal to it; and if the strain of *T. rhodesiense* freshly isolated from man was resistant to human serum, previous experiments having shown that freshly isolated strains of *T. rhodesiense* were more resistant to human serum than strains which had been maintained in sheep and goats for several months after isolation from man. The technique employed was based on that of YORKE, ADAMS & MURGATROYD (1930). The results, which are summarized in a table, show that the guineapig serum had no apparent trypanocidal action on *T. brucei*, Tanganyika, and that the serum of the resistant rat had also none on *T. brucei* Natal. Both strains of *T. brucei* were susceptible to normal serum as was also the strain of *T. rhodesiense*. *W. Y.*

JOHNSON (P. D.) **A Case of Infection by** *Trypanosoma lewisi* **in a Child.** —*Trans. Roy. Soc. Trop. Med. & Hyg.* 1933. Mar. 23. Vol. 26. No. 5. pp. 467–468. With 1 chart.

In this very interesting note details are given of an instance of infection of a human being by *Trypanosoma lewisi*.

The patient was a Sikh child born in Batu Gajah Hospital, Federated Malay States, on the 5th April, 1932. A week later the child was taken to its father's house, which was a rat infested dwelling. It is stated that the rats ran over the children's beds and ate any food that was not locked up. On August 22nd the child was re-admitted to hospital with a history of lassitude and loss of appetite for three weeks, and fever for ten days. The child was very anaemic; the liver and spleen were not palpable; the blood was negative for malaria parasites, but was heavily infected with trypanosomes which had the typical appearance of *T. lewisi*. The parasites persisted in the peripheral blood for five days, but from the 6th day onwards blood films were negative. The fever subsided coincidentally with the disappearance of trypanosomes from the blood.

It is remarked that blood films were sent to Professor THOMSON and to Dr. WENYON, who both stated that the trypanosomes on the slide in question were *T. lewisi*. Attempts to convey the infection to rats and guineapigs, after its passage through the child's blood, proved unsuccessful. *W. Y.*

GREIG (E. D.). **Notes on Recent Cases of Trypanosomiasis** (*T. gambiense*).— *Jl. Trop. Med. & Hyg.* 1933. Jan. 16. Vol. 36. No. 2. pp. 23–24.

Details are given of a case of sleeping sickness—the wife of a missionary in Southern Nigeria—who, although very ill, was admitted to hospital in

Edinburgh and made an excellent recovery as the result of combined therapy consisting of 5 gm. of Bayer 205 and 25 gm. of tryparsamide.

W. Y.

HISSETTE (J.). Considérations pratiques sur des accidents oculaires de la trypanosomiase ou de son traitement. [**Eye Symptoms in Trypanosomiasis.**]—*Ann. Soc. Belge de Méd. Trop.* 1932. Dec. 30. Vol. 12. No. 4. pp. 531–538.

This article considers the eye changes met with in human trypanosomiasis and their bearing upon treatment.

Among the external complications are (1) a benign endocyclitis, (2) a diffuse interstitial keratitis, (3) conjunctivitis with secretion, and (4) oedema of the lids without renal or cardiac disease. The first two conditions seriously interfere with vision, especially if they are bilateral. Evidently then, when a sleeping sickness patient complains of his sight, it is necessary to examine the eyes carefully, as failure to do so may wrongly cause suspension of treatment. It is not necessary to be able to distinguish trypanosomal interstitial keratitis from that due to syphilis, leprosy or onchocerca, but it is necessary to realize that the loss of vision is due to an external trouble and not to a nerve lesion.

Turning to the complications of the posterior portions of the eye and optic nerve there have been described a form of choroiditis (Treacher Collins) and a pigmented choroidoretinitis ; both these are rare. The most important are undoubtedly the different kinds of atrophy of the optic nerve. These are two : (1) a primary atrophy, and (2) a secondary atrophy. The clinical signs of these are identical with those of the atrophy due to arsenical poisoning. It is important, therefore, when a diagnosis of sleeping sickness is made, not to forget to examine the visual acuity of each eye separately. The examination of the visual field, the value of pupillary reflexes, etc., and the ophthalmoscopic appearances are matters for the specialist. Much valuable information could be obtained from a carefully ascertained history, but in the case of Africans this necessitates a knowledge of the language, which is well-worth acquiring by those engaged in treating natives.

In the author's experience optic atrophy as the result of tryparsamide, or the Belgian equivalent tryponarsyl, is very rare, provided the drug is given as recommended by VAN DEN BRANDEN. If careful examination of the eye suggests that this is occurring, the arsenical must be stopped and tartar emetic given. The author considers that it is important to examine the patient carefully for dysentery and worms, and to prohibit alcohol and tobacco, because not only may these produce analogous conditions, but they may aggravate the toxic action of arsenicals.

Hissette then passes to a consideration of eye changes which may result from Onchocerca. These changes evolve slowly, and the patients almost always exhibit volvulus cysts ; they often manifest themselves as a kerato-conjunctivitis or as a punctate keratitis. In other cases, however, these signs are absent and the lesions are confined to the posterior segment of the eye ; there may be atrophy with pallor of the disc, or the trouble may be retro-bulbar. Arsenical atrophy sets in rapidly, whilst retrobulbar trouble due to Onchocerca develops very slowly.

In conclusion, the author remarks that he has used tryponarsyl extensively in the treatment of trypanosomiasis, according to van den

Branden's method, and that among more than 2,000 patients he has had only one case of partial atrophy in one eye. The cases of complete optic atrophy seen by him were generally produced by atoxyl.

W. Y.

WORMALL (Arthur). **Carbohydrate Metabolism in Human Trypanosomiasis.**—*Biochem. Jl.* 1932. Vol. 26. No. 6. pp. 1777–1787. [29 refs.]

After summarizing briefly the literature relating to carbohydrate metabolism in experimental trypanosomiasis, the author points out that so far no observations appear to have been made on the blood-sugar changes in human trypanosomiasis. The present paper records observations on the resting blood sugar values and the sugar tolerance for natives with trypanosomiasis and the values for normal natives. The observations are set forth in a series of tables.

The following summary is given :—

" 1. In view of the findings of various authors, that in trypanosomiasis of small animals there is a significant hypoglycaemia, which according to some is partially, if not entirely, responsible for the decline of the host, repeated blood-sugar determinations have been carried out on 12 sleeping sickness patients in Uganda (*T. gambiense* infections).

" 2. Determinations carried out with these patients and with suitable controls (natives not suffering from trypanosomiasis) over varying periods of time indicate that in man there is no general hypoglycaemia during the earlier stages of this disease. In certain instances, however, a definitely low blood-sugar value was obtained, these low values being significantly lower than the lowest value with a normal native.

" 3. Treatment of these patients with Bayer 205 gives variable results in relation to the blood-sugar ; sometimes there is a fall, sometimes a rise, and in other cases no change in the blood-sugar level. With the patient with the lowest blood-sugar values, the injection of 1 g. Bayer 205 resulted in a speedy return to normal (or perhaps slightly high) values.

" 4. No relationship could be demonstrated between the blood-sugar level and the presence in or absence from the blood of trypanosomes.

" 5. Glucose tolerance tests carried out on a few of the patients and some of the controls do not suggest that in trypanosomiasis there is a very marked impairment of the capacity of the liver to deal with glucose. *W. Y.*

LAURENT (R.). Remarques à propos de l'action du traitement par la tryparsamide, sur la lymphocytose du liquide cephalorachidien, au cours de la trypanosomiase. [**Effect of Tryparsamide on Lymphocytosis of the C.S.F. in Trypanosomiasis.**]—*Ann. Soc. Belge de Méd. Trop.* 1932. Dec. 30. Vol. 12. No. 4. pp. 539–544.

The author records his observations on the effect of tryparsamide treatment on the lymphocyte count of the cerebrospinal fluid in a large number of cases of sleeping sickness. The work has been carried out at Lomami since 1931.

With very few exceptions tryparsamide was the only drug given. The standard-cure consisted of 30 gm. of tryparsamide (tryponarsyl Meurice) given in 15 weekly doses of 2 gm. Lumbar puncture was done before and after treatment. Patients in whom the spinal fluid was normal 2 to 3 months after treatment were considered as apparently cured, but ought to be re-examined every 6 months. Those in whom the spinal fluid still contained an excess of cells were given further

courses until the number of lymphocytes fell to normal. Only two cases of blindness were encountered and both had previously, in 1928, been treated with atoxyl-emetic. The results are summarized as follows :—

Group I. Spinal fluid pathological before treatment=166 cases.

A. Patients with normal fluid after treatment=148 (89·15%) ; of these 76 were normal after a single course, and 72 after several courses.

B. Patients with condition of spinal fluid improved=10 (6·02 per cent.), 9 after a single course and 1 after several courses.

C. Patients with spinal fluid unchanged=8 (4·81 per cent.) ; 2 after 1 cure and 6 after several cures.

Group 2. Spinal fluid normal before treatment=153 cases.

A. Patients with normal fluid after treatment=150 (98·03 per cent.) ; 141 after a single cure and 9 after several cures.

B. Patients with abnormal spinal fluid=3 (1·96 per cent.).

Group 3. Spinal fluid not examined before treatment=141 cases.

A. Patients with normal spinal fluid after treatment=116 (82·26 per cent.); 47 after a single cure and 69 after several cures.

B. Patients with abnormal spinal fluid after treatment=25 (17·73 per cent.) ; 19 after a single cure and 6 after several cures.

From these figures it is concluded that in the great majority of cases tryparsamide treatment within a few months results in the production of a normal spinal fluid ; and in cases with normal spinal fluid it prevents the development of pathological changes. This result is often obtained from a single course of the drug.

In comment on this paper RODHAIN points out that the action of the drug at Lomami appears to be superior to its action in other parts of Africa. Possibly the strain of *T. gambiense* is peculiarly sensitive to arsenicals. The ultimate fate of the patient is a matter of great interest. *W. Y.*

BARLOVATZ (A.). Des réactions méningées consécutives au traitement, dans la maladie du sommeil. [**Meningeal Reactions in Sleeping Sickness following Treatment.**]—*Bruxelles-Méd.* 1933. Apr. 16. Vol. 13. No. 24. pp. 659–661.

The author draws attention to the meningeal reactions which are sometimes observed after the administration of various trypanocidal medicaments. He gives details of two cases in which both the number of cells and albumin content of the cerebrospinal fluid increased materially after a couple of subcutaneous injections of atoxyl.

He points out that these cases have not been selected. He believes that of 100 with normal cerebrospinal fluid treated in this way 70 are found to be cured after a year, and about 25 are sterilized, but show signs of evolution of nervous lesions ; in other words, the great majority of the non-cured show, after a lapse of time, altered cerebrospinal fluid, and this occurs more rapidly than in patients who remain untreated.

Details are next given of a case treated by tryparsamide and Bayer 205. Before treatment the cerebrospinal fluid showed 18 leucocytes per cmm. and a normal albumin content. On the 12th April, 1932, 2 gm. of tryponarsyl was given, and then, between 16th April and the 13th June, 10 gm. of tryponarsyl and 1·3 gm. of Bayer 205. Treatment was interrupted because the patient had become suddenly blind. On the 1st August the cerebrospinal fluid contained 600 leucocytes per cmm. and the albumin content had increased to 0·32. On the 8th

December lumbar puncture showed 19 leucocytes and a normal albumin content. She was then given 5 weekly injections of 0·7 gm. tryparsamide. On the 21st February, 1933, lumbar puncture showed 13 leucocytes and a normal albumin content ; the blood and lymphatic glands were sterile.

The author remarks that reactions of this nature are exceptional after tryparsamide.

Similar meningeal reactions were seen with chloro-methylate of diamino-acridine [? trypaflavine]. *W. Y.*

VAN DEN BRANDEN (F.) & DUBOIS (A.). Influence d'une infection syphilitique antérieure sur les résultats du traitement de la maladie du sommeil. [**Influence of Old Syphilitic Infection on Treatment of S.S.**]—*Ann. Soc. Belge de Méd. Trop.* 1932. Dec. 30. Vol. 12. No. 4. pp. 557–567.

The authors discuss the influence of an old-standing syphilitic infection on the treatment of subsequently acquired trypanosomiasis.

Brief details, relating to the condition of the spinal fluid, and treatment with tryponarsyl, are given in respect of 26 patients, in all of whom the Wassermann reaction was strongly positive. The patients are divided into three groups : viz., those who were greatly benefited by treatment, those who were improved, and those who were not improved.

In commenting on these cases it is noted that a definite diagnosis of trypanosomiasis was made by the discovery of the trypanosomes, usually in the lymphatic glands. The patients were judged to be in the second stage of the disease, either because of the clinical condition or as the result of spinal puncture. The reasons for believing that they had all suffered from syphilis are discussed at length.

Among the 26 cases studied there were 14 successes (excluding the 5 cases who were improved). This figure, 50 per cent., agrees with that usually obtained in the treatment of second stage cases of sleeping sickness ; and consequently, the authors conclude that the presence of syphilis does not appreciably aggravate the prognosis in trypanosomiasis, nor does it increase its resistance to therapy. *W. Y.*

DUBOIS. Sur la thérapeutique de l'infection à trypanosome " congolense " (Broden), par le Bayer 205 et l'émétique de potassium associés. [**Treatment of** *T. congolense* **Infection by Bayer 205 and Tartar Emetic in Association.**]—Reprinted from *Bull. Inst. Roy. Colonial Belge.* 1930. Vol. 1. No. 2. pp. 326–335.

The paper supports the view that Bayer 205 and tartar emetic together give better results in the treatment of *T. congolense* infections than does either drug given alone.

The strain of *T. congolense* used came from Leopoldville and had been kept for 3 years in guineapigs at Brussels. It now kills these animals in 9 to 11 days. The various experiments are summarized in a table from which it appears that a relapse always occurred after the administration of either drug given alone, but a number of cures followed the administration of the two drugs together.

The following are the conclusions :—

1. Our experiments confirm the real value of the combined Bayer 205-emetic treatment in guineapigs infected with *T. congolense*. Whether all strains of *T. congolense* and all animals are favourably influenced experience alone will show.

2. It is necessary to give high doses of tartar emetic.
3. The curative mechanism is obscure. It is not at present possible to consider as demonstrated the antimutative action described by Morgenroth.
4. Tryparosan *per os*, in doses of 700 mgm. per kilo. in two days, produced cure in two animals. *W. Y.*

DUBOIS (A.). Note préliminaire sur l'action thérapeutique d'un nouveau dérivé antimonial. [**Therapeutic Action of a New Antimonial Derivative.**]—9 pp. Congrès National des Sciences. [No place or date of publication.]

A preliminary report is given regarding the therapeutic activity of a new antimonial compound, Dn6, on guineapigs, rats and mice infected with either *T. congolense* or *T. pecaudi*.

The compound is stated to be antimonyl-bis-orthooxyquinoline-anasulphonate of diethylamine. It is less toxic than tartar emetic, the tolerated dose on subcutaneous injection being 150 mgm. per kilo. as compared with about 10 mgm. for emetic ; in intravenous injection the tolerated dose is less, probably about 60 mgm. The exact dosage of the medicament has not yet been determined precisely. It is too irritating to permit of its subcutaneous or intramuscular administration in man.

The drug had no action on *Spirochaeta hispanica* in guineapigs, but it was active against the pathogenic trypanosomes. Its action was superior to that of tartar emetic, and this fact, in the author's opinion, warrants its trial in trypanosomiasis of the domestic animals or even of man. *W. Y.*

LAUNOY (L.). Documents statistiques pour servir à l'étude du mécanisme des actions synergiques chimiques trypanocides, dans lesquelles intervient le 205 Bayer-309 Fourneau. [**Study of Mechanism of Synergic Action of Bayer 205-Fourneau 309.**]—*C. R. Soc. Biol.* 1933. Feb. 10. Vol. 112. No. 5. pp. 448–451. With 2 figs.

In analysing the mechanism of synergic actions it is necessary to know how the infected animals respond when subjected to each of the factors separately. With this object in view, the author has attempted to study the effect of a non-curative dose of " Bayer 205 " on mice infected with *T. congolense*.

In his experiments he used 93 mice : these were divided into two batches, the first of which consisting of 47 mice was inoculated with *T. congolense* and the infection allowed to run its normal course ; the second batch consisting of 46 mice was inoculated with *T. congolense*, and, when parasites had appeared in the blood, each animal was given a non-curative dose of 0·005 gm of Bayer 205 per 20 gm. of mouse.

The courses of the infection in the two batches of mice were then compared ; in the first batch the observation commenced at the time of the first appearance of trypanosomes in the blood, and in the second batch at the time of the appearance of the relapse parasites. Details are given regarding the incubation period, and time of death in the animals comprising each series and the results are shown in graphs. In the untreated batch the great majority of the animals had died within 10 days of the first appearance of trypanosomes in the blood ; in the treated batch the length of life counting from the time of the appearance of the relapse parasites in the blood is greatly prolonged in at least 60 per cent. of the mice. *W. Y.*

ABONDANO (Herrera Alberto). Contribution à l'étude de la chimiothérapie des trypanosomiases. Note préliminaire. [**Chemotherapy of Trypanosomiasis.**]—*Boll. Sezione Ital., Soc. Internaz. di Microbiologia.* Milan. 1932. Nov. Vol. 4. No. 11. pp. 413–414.

The author claims to have shown that a combined treatment consisting of picric acid and arsenobenzol gives better results in mice infected with *T. brucei* than does arsenobenzol alone.

The minimal lethal dose of picric acid for healthy mice is 20 cgm. per kilo., and for infected mice 10 cgm. per kilo. This drug given alone to infected mice had no action, nor had arsenobenzol (Pieroni) when given in doses of 5 cgm. or less per kilo. But when picric acid was given in association with the arsenobenzol a definite therapeutic effect was noticed. With another preparation (Néoiacol) still better results were obtained. It is further remarked that, as ZIRONI has already pointed out, the very stable arsenobenzol "bicopulé" (Pieroni) is much less active than is the less stable arsenobenzol "monocopulé."* *W. Y.*

DORTMANN (Heinrich). Studien ueber das Zustandekommen des trypanoziden Effektes bei verschiedenen Stoffen. [**Studies on the Trypanocidal Effects of Different Substances.**]—*Ztschr. f. Immunitätsf. u. Experim. Therap.* 1932. Vol. 77. No. 5/6. pp. 403–420. [61 refs.]

The following summary is given :—

1. The autolysate of certain bacteria is able to kill *T. equiperdum in vitro.* The autolysate of the hay bacillus has a particularly powerful trypanocidal action, whilst that of the Wurzel bacillus A is less active. The degree of the trypanocidal action of these substances is dependent on the duration of the autolysis; the longer it is, the greater the trypanocidal action. The autolysates of the other bacteria examined exhibited no trypanocidal action.

The filtrates of broth cultures of various bacteria may possess trypanocidal properties. The filtrate of the *Bacillus subtilis* is but slightly active, whereas that of *Bacillus pyocyaneus* is very potent.

In animal experiments the bacterial products exhibit no trypanocidal action. Apparently the action of the bacteria within the animal body is nullified by certain protective functions of the animal organism. Previous treatment of mice with the autolysate of *Bacillus subtilis* sufficed to enhance slightly the resistance of the animals to subsequent infection with *T. equiperdum*, as also did vaccination with *Bacillus coli* or *Bacillus typhosus*.

2. The combination of normal human serum with dyes (argoflavin and trypanblue) results in a definite increase of the trypanocidal action of the single components. The combination of human serum and trypanblue is especially active and can produce definite cures. This powerful effect suggests the possibility of some direct action beyond the indirect effect of the single components.

The combination of normal human serum with antimosan gives on the contrary no better results than the single components.

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*In an article published in 1924 ZIRONI† calls attention to the work of CONTARDI and CAZZANI who divide arsenobenzol derivatives of 606 into three groups, A, B and C. In the first are two series of products: one with a single amino group joined to the acid residue, the other with both amino-groups so united. It would appear from the above that the product with the single group (monocopulé) parts with it more readily than does the other, with two groups (bicopulé), in the presence of picric acid.

†ZIRONI (Amilcare). Contributo allo studio del potere terapeutico e della tossicità degli arsenobenzoli. Parte Prima. Gli arsenobenzoli nella terapia di infezioni tripanosomiasiche.—*Boll. Istituto Sieroterap. Milanese.* 1924. Aug. Vol. 3. No. 5. pp. 289–329.

3. The preparations "Euthagen" [a silver compound] and hexylresorcin exert *in vitro* a definite trypanocidal action, but this is not manifest in animal experiments. *W. Y.*

i. YORKE (Warrington), MURGATROYD (Frederick) & HAWKING (F.). **Studies in Chemotherapy. VIII. Comparison of Strains of *T. rhodesiense* made Resistant to Various Arsenicals and Antimonials, to Bayer 205, and to Acriflavine, respectively.**—*Ann. Trop. Med. & Parasit.* 1932. Dec. 16. Vol. 26. No. 4. pp. 577–586.

ii. ——, —— & ——. **Studies in Chemotherapy. IX. Sodium Thiosulphate and Arsenic-Resistance.**—*Ibid.* pp. 587–596.

i. The last paper of this series was noticed above, page 111. The series deals with drug resistance.

The authors have already shown that a strain of *T. rhodesiense* made resistant to atoxyl is indistinguishable from a strain of the same parasite made resistant to acriflavine. The two strains exhibited marked resistance to all the aromatic compounds of arsenic and antimony and to acriflavine, but were as sensitive to sodium arsenite, tartar emetic, and Bayer 205 as the normal strain. The authors now inquire whether it is also possible by treatment of infected animals with subcurative doses of the other commonly employed aromatic arsenical and antimonial compounds, of tartar emetic, and of Bayer 205 to produce resistant strains and whether the resulting strains are similar to the atoxyl-fast and acriflavine-fast strains. Their conclusions are adequately stated in their summary :—

"1. The object of the work described in this paper was, firstly, the preparation of a number of strains resistant to various drugs, and secondly, the comparison of the resulting resistant strains to see how far they differed from one another and from the normal parent strain.

"The normal strain used was an old laboratory strain of *T. rhodesiense*, and the technique employed in the endeavour to produce the resistant strains was the customary one of treating mice infected with the normal strain with subcurative doses of the drugs, and gradually increasing the doses as relapses occurred in the original mice and in those of later passage. The compounds to which it was attempted to produce resistant strains were :—

"A. *Aromatic compounds of arsenic.*—Atoxyl, arsacetin, tryparsamide, reduced tryparsamide thioglycollate, halarsol, novarsenobillon and arsenophenylglycine.

"B. *Aromatic compound of antimony.*—Stibenyl.

"C. *Non-aromatic compound of antimony.*—Tartar emetic.

"D. *Acriflavine.*

"E. *Bayer* 205.

"2. By this procedure it was found possible to produce resistant strains with every drug, except tartar emetic.

"3. The speed with which resistant strains were produced varied considerably. With atoxyl, arsacetin, tryparsamide, reduced tryparsamide thioglycollate, stibenyl and acriflavine, highly resistant strains were produced within 4 to 8 weeks. The production of halarsol- and novarsenobillon-fast strains required a period of about 3 months; the arsenophenylglycine-fast strain developed still more slowly; and the Bayer 205-fast strain did not attain to its maximum degree of resistance until after more than 12 months. For reasons stated, however, it is possible that to some extent these differences may be more apparent than real.

"4. Comparison of the resulting strains showed that they could be arranged into the following 4 groups :—

"(*a*) Strongly resistant to the aromatic compounds of arsenic (except arsenophenylglycine) and of antimony; slightly resistant to arsenophenylglycine; sensitive to tartar emetic and to Bayer 205, viz., *atoxyl-fast,*

arsacetin-fast, tryparsamide-fast, reduced tryparsamide-fast, halarsol-fast, novarsenobillon-fast, and *acriflavine-fast* strains.

" (*b*) Resistant to arsenophenylglycine; moderately resistant to the other aromatic arsenicals and antimonials; sensitive to tartar emetic and to Bayer 205, viz., *arsenophenylglycine-fast* strain.

" (*c*) Similar to Group A, but resistant to tartar emetic, viz., *stibenyl-fast* strain.

" (*d*) Strongly resistant to Bayer 205; sensitive to all the other drugs, viz., *Bayer* 205-*fast* strain.

" 5. These facts appear to admit of the following generalizations:—

" (*a*) Resistance to Bayer 205 does not involve resistance to arsenical or antimonial compounds, and conversely resistance to the latter does not mean resistance to the former.

" (*b*) Resistance to an aromatic arsenical or antimonial compound implies resistance to other aromatic arsenicals and antimonials; but this does not necessarily mean that a strain made resistant to one aromatic arsenical is identical with that made resistant to another, *vide* the differences in degrees of resistance exhibited by a tryparsamide-fast strain and a strain made resistant to arsenophenylglycine.

" (*c*) A strain made resistant to an aromatic arsenical is sensitive to tartar emetic, whereas a strain made resistant to an aromatic antimonial is resistant to tartar emetic. This fact calls for special comment. Although it is extremely difficult, or even impossible, to produce a tartar emetic-resistant strain by the ordinary direct method of administering sub-curative doses of the drug to mice infected with the normal strain, it is exceedingly easy to produce a resistant strain by the indirect method of first producing an atoxyl-resistant strain and then acting upon it with tartar emetic. There is evidence to believe that stibenyl, like the other aromatic antimonial compounds, readily undergoes a certain amount of decomposition when introduced into the animal body; and we believe that the mechanism, whereby a stibenyl-fast strain becomes emetic-fast, is similar to that whereby an atoxyl-fast strain can subsequently be made emetic-fast."

The authors draw attention to the ease with which a strain resistant to atoxyl may be made resistant to tartar emetic: two or three doses sufficed for mice. They think it may have an important bearing on atoxyl plus tartar emetic treatment in man.

ii. CITRON claims to have destroyed the resistance of a salvarsan-fast strain of trypanosomes by prolonged treatment of a series of infected mice with sodium thiosulphate [see this *Bulletin*, Vol. 28, p. 912]. The authors repeated this work and give details of their experiments which those interested will consult. Their attempts to influence the resistance of atoxyl-fast and novarsenobillon-fast strains of *T. rhodesiense* (*a*) by repeated administration of sodium thiosulphate to series of infected mice, and (*b*) by repeated exposure of these strains to concentrated solution of sodium thiosulphate *in vitro* were fruitless. Hence they were unable to confirm CITRON. *A. G. B.*

YORKE (Warrington), MURGATROYD (Frederick) & HAWKING (Frank). **Effect of Passage through Glossina on the Resistance of a Tryparsamide-fast Trypanosome.**—*Brit. Med. Jl.* 1933. Feb. 4. pp. 176–179.

——, —— & ——. **Studies in Chemotherapy. X. Further Observations on the Transmissibility of Tryparsamide-Resistance by Glossina.**—*Ann. Trop. Med. & Parasit.* 1933. Apr. 10. Vol. 27. No. 1. pp. 157–178.

In these papers it is shown that a strain of trypanosomes (*T. brucei*) possessing a high degree of resistance to the aromatic arsenicals, when

transmitted by Glossina maintained its resistance unimpaired even after two successive passages through the fly.

The importance of drug-resistance is stressed, and especially the question whether a drug-resistant strain is still drug-resistant after cyclical development in its insect host. The problem has been studied by WERBITZKI and GONDER (1911), by REICHENOW and REGENDANZ (1927) and by DUKE (1927) [see this *Bulletin*, Vol. 24, p. 947 and Vol. 25, p. 349]; the experiments failed to solve it satisfactorily because there is reason to believe that their so-called resistant strains were little, if any, more resistant than the parent strains.

The authors at Liverpool obtained pupae by air-mail of *G. morsitans* from Tanganyika and of *G. palpalis* from Uganda. The trypanosome was a strain of *T. brucei* obtained from a dog in Ankole, Uganda, in April, 1931, and since maintained in guineapigs. It is a polymorphic trypanosome with numerous posterior nuclear forms. The response of this strain in mice and guineapigs to various arsenicals was ascertained; *e.g.*, it was found that the minimum effective dose of tryparsamide for guineapigs was 0·05 gm. per kilo. Details of these experiments are tabulated. An infected guineapig was treated from September to November with repeated small, but gradually increasing, doses of tryparsamide and finally 0·5 gm. failed to clear the blood of parasites. The strain was then submitted to arsenicals in subinoculated guineapigs and mice and was found to resist the maximum doses tolerated by these animals.

Transmission experiments.—Three experiments were made, each with *G. palpalis* and *G. morsitans* fed on infected guineapigs and afterwards on a series of healthy guineapigs. In No. 1 the normal parent strain was successfully transmitted; in No. 2 the branch of the strain made resistant to tryparsamide, and in No. 3 the same strain after passing through Glossina in No. 2. A table gives the details. In each experiment at least one fly was found to have gut and salivary glands infected. In the three experiments of 205 *palpalis*, alive at the first feed on the clean animal, 9 (4·5 per cent.) showed infection of gut only, and 3 (1·5 per cent.) infection of gut and salivary glands; and of 87 *morsitans* 9 (10·4 per cent.) showed infection of gut and 4 (4·6 per cent.) infection of gut and salivary glands.

The response of the transmitted strains to arsenicals was then tested. The table shows the minimum effective dose of various drugs for mice infected with the normal and tryparsamide-resistant strains before and after transmission by Glossina.

Drug.	Normal Strain.		Tryparsamide-resistant strain.		
	Parent.	After passage through Glossina.	Parent.	After one passage through Glossina.	After two passages through Glossina.
Tryparsamide ...	8	6–10	45+	45+	45+
Reduced Tryparsamide	0·06–0·1	0·08	2+	2+	2+
Arsacetin	3	4	30+	30+	30+
Halarsol	0·03	0·03	0·6+	0·6+	0·6+

N.B.—The figures represent milligrams of drug per 20 gm. of mouse.

The author's conclusions follow :—

" 1. In this paper a detailed account is given of experiments devised with the object of ascertaining whether a tryparsamide-fast strain of trypanosomes is transmissible by Glossina, and if so whether its resistant character persists after passage through the fly.

" 2. The trypanosome used was a strain of *T. brucei*, isolated from wild *G. morsitans* in Uganda in 1931, and subsequently maintained in the laboratory by passage through guinea-pigs for a period of 18 months. Careful examination of the strain showed that in so far as its morphology and pathogenicity were concerned it was indistinguishable from other strains of *T. brucei* recently isolated from Glossina : this implies that the strain had undergone no discoverable change during its 18 months' sojourn in guinea-pigs. The response of the strain to arsenicals was then carefully determined : in guinea-pigs the M.E.D. of tryparsamide was about 0·05 gm. per kilo ; and in mice the M.E.D. of tryparsamide was 8 mgm., of reduced tryparsamide 0·06 to 0·1 mgm., of arsacetin 3 mgm., and of halarsol 0·03 mgm. per 20 gm.

" 3. The tryparsamide-resistant variety was made by repeated administration of gradually increasing doses of the drug to an infected guinea-pig ; eventually the resistance of the strain was increased to a point when it withstood the maximum dose well-tolerated by a guinea-pig, *i.e.*, about 10 times the M.E.D. for the normal strain. It is of importance to note that this change in drug-resistance was not accompanied by any change in morphology or pathogenicity. Experiments showed that in guinea-pigs this resistant strain withstood 0·5 gm. of tryparsamide per kilo ; and in mice 45 mgm. of tryparsamide, 2 mgm. of reduced tryparsamide, 30 mgm. of arsacetin and 0·6 mgm. of halarsol per 20 gm. From this it follows that the strain resisted the maximum doses of the various drugs tolerated by the vertebrate hosts.

" 4. In the transmission experiments both *Glossina palpalis* and *Glossina morsitans* were used. The insects were sent to this country in the pupal state by air mail. An account is given of the methods employed for the maintenance of the flies in the laboratory, and of the technique adopted for the transmission experiments.

" 5. Transmission experiments were successful with :—

" (i) The normal parent strain.

" (ii) The Tryparsamide-resistant branch of the parent strain. (1st fly-passage).

" (iii) The Tryparsamide-resistant branch which had already been once transmitted by Glossina (2nd fly-passage).

" Some evidence was obtained which suggests that the strain of *T. brucei* used was more easily transmissible by *G. morsitans* than by *G. palpalis*.

" 6. The transmitted strains were carefully examined as regards their morphology, pathogenicity and response to arsenicals. It was found that in none of these respects had the two strains been modified as the result of their passage through Glossina.

" The normal strain after passage through Glossina was just as sensitive to arsenicals as it had been previously, and similarly two successive passages of the resistant-strain through Glossina had in no degree lessened its resistant characters.

" 7. These experiments afford, in our opinion, conclusive proof that :—

" (i) Strains of trypanosomes possessing a high degree of resistance to the aromatic arsenicals are transmissible by Glossina.

" (ii) The acquired character of drug-resistance is unimpaired after two successive passages through Glossina." *A. G. B.*

LESTER (H. M. O.). **The Influence of Cyclical Transmission by *Glossina tachinoides* on a Strain of *Trypanosoma brucei*, made Resistant to Human Serum.**—*Ann. Trop. Med. & Parasit.* 1932. Dec. 16. Vol. 26. No. 4. pp. 525–537. With 1 diagram. [15 refs.]

In this paper the author gives an account of experiments devised with the object of ascertaining whether the acquired character of serum resistance in a strain of *T. brucei* was preserved after passage through *G. tachinoides*.

The strain of *brucei* used was isolated from *G. morsitans* in May, 1930. When the experiments were commenced it was five months old and had been maintained by direct transmission through a series of 3 dogs and 3 rhesus monkeys When freshly isolated the strain was somewhat avirulent, but the direct transmissions had exalted its virulence to such an extent that it killed small laboratory animals—guineapigs, rats and mice—in a few days. The parasite was made resistant to human serum by treating infected mice with repeated doses of serum. The strain was then returned to a guineapig, which was subsequently given an intraperitoneal injection of 6 cc. of serum. This dose cleared the peripheral blood of the guineapig in a few hours, and on subsequent passage into a mouse the strain was found to have lost a considerable portion of its serum resistance. Consequently, further treatment was necessary before the strain became sufficiently serum fast for the fly transmission to be attempted. A stage was eventually reached at which the trypanosomes in the mouse were fast to 1 cc. of human serum even after intermediate passage through the guineapig.

Details of the transmission experiments are given in a diagram, and a table shows that the trypanosome was resistant to human serum after cyclical passage through the tsetse.

The following summary is given :—

" 1. As a result of their discovery of the trypanocidal action, *in vitro*, of normal human serum, Yorke, Adams & Murgatroyd elaborated a hypothesis regarding the epidemiology of rhodesiense and gambiense sleeping sickness. They postulate that, although *T. rhodesiense* is identical with *T. brucei*, normal human beings cannot be infected with the game trypanosomes because of the trypanocidal power of their serum. In certain pathogenical conditions the blood of man loses its trypanocidal power, allowing the game trypanosomes to become established.

" 2. If this hypothesis is correct, the serum-fast character, once it has been acquired by the game trypanosomes, must be preserved during cyclical transmission by tsetse. In order to throw some light on this point, a strain of *T. brucei*, originally quite serum-sensitive, was kept in mice which were treated with repeated doses of normal human serum. When once the strain became serum-fast it was passed by cyclical transmission through *G. tachinoides*. On testing again the reaction of the strain to human serum, it was found that the acquired serum-resistance had been preserved through the fly.

" 3. After cyclical transmission the virulence of the strain to small laboratory animals had diminished very greatly. This was particularly well shown in mice. Before cyclical transmission, the behaviour of the strain was in accordance with the classical description. Trypanosomes appeared in the blood after a short incubation period, and increased in number steadily until the death of the mouse. After passing through tsetse there was a long incubation period, trypanosomes were never at all numerous in the blood, and there were numerous relapses. Several mice lived more than six months, showing only an occasional scanty infection in the blood. In view of these observations it is difficult to

believe that the mouse can have no defensive mechanism against the pathogenic trypanosomes.

"4. The doubt arises as to whether much of the work done with old laboratory strains, the characteristics of which have been changed by constant syringe passage, can give a true picture of what occurs in nature."

W. Y.

TRENSZ (F.) & JARDON (M.). Les protides du sérum et la réaction de Henry dans la trypanosomiase expérimentale. (Note préliminaire.) [**Serum Proteids and Henry's Reaction in Experimental Trypanosomiasis.**]—*Bull. Soc. Path. Exot.* 1933. Mar. 8. Vol. 26. No. 3. pp. 442–444.

The researches show that in so far as the serum proteins are concerned there is a similarity between experimental trypanosomiasis, malaria, and kala azar.

The authors have estimated the amount of euglobulin in the serum of guineapigs and rabbits infected with *T. berberum* and have compared the results with those obtained in normal animals. In 19 normal guineapigs the average amount of euglobulin in the serum was 0·44 gm. per litre. In 41 infected guineapigs there was a slight increase in the euglobulin within 8 to 10 days after inoculation; at this time Henry's reaction was doubtful. As the disease progressed the titre of euglobulin steadily increased, Henry's reaction became quite definite, and the serum acquired the property of flocculating in distilled water. It is noted that the 13 doubtful Henry reactions corresponded to an average euglobulin titre of 0·83 gm. per litre; in the 20 positive Henry reactions the amount of serum euglobulin was 2·15 gm. per litre; in the 4 cases with strongly positive Henry reactions the euglobulin was 3·71 gm. per litre; and in 4 with massive Henry reactions the euglobulin was 8·1 gm. per litre. The sera giving the strongest Henry reactions flocculated in distilled water.

It appears therefore that Henry's reaction is always associated with a hypereuglobulinaemia, but the reverse is not always true.

W. Y.

NATTAN-LARRIER (L.) & NOYER (B.). Vitalité et résistance des trypanosomes métacycliques. [**Vitality and Resistance of Metacyclic Trypanosomes.**]—*C. R. Soc. Biol.* 1933. Apr. 10. Vol. 112. No. 13. pp. 1276–1279.

The author describes the resistance of the leptomonas forms and the metacyclic forms of *Trypanosoma rabinowitchi*. Cultures were made on blood agar, and after incubation at 38°C. for 48 hours a rich growth containing both forms was obtained. With this material it was easy to compare the vitality of the two forms under various physical and chemical conditions. The work shows that the metacyclic forms are definitely more resistant than are the leptomonas forms. *W. Y.*

DUKE (H. Lyndhurst). **The Polymorphic Trypanosomes of Damba Island, Victoria Nyanza. II.—Their Transmissibility by** *G. palpalis.*—*Ann. Trop. Med. & Parasit.* 1932. Dec. 16. Vol. 26. No. 4. pp. 597–601.

This paper is concerned with the transmissibility by *G. palpalis* of three strains of trypanosomes obtained from wild *G. palpalis* on Damba Island in 1932. Details of the experimental work are given in tables.

The following is the summary.

"1. One of the three 1932 strains of the Damba trypanosome, No. 912, was on its first isolation considerably more transmissible by *G. palpalis* than the other two strains.

"2. The transmissibility of this strain is higher than the majority of *T. gambiense* strains examined, and approaches the standard commonly reached by *T. rhodesiense* strains in the experiments carried out at Entebbe over a number of years.

"3. Strain 912 is more readily transmissible by *G. palpalis* than any other strain previously isolated from *Tragelaphus spekei* on Damba Island."

W. Y.

DUKE (H. Lyndhurst). **Infection Rate of *Glossina* and Temperature.** [Correspondence.]—*Trans. Roy. Soc. Trop. Med. & Hyg.* 1933. Mar. 23. Vol. 26. No. 5. p. 481.

In this letter Duke states that he wishes to remove the misunderstanding which might arise as a result of TAYLOR's quotation of his (Duke's) reference to LLOYD's use of incubator temperatures as "artificial and enervating." Duke writes as follows :—

"My attitude, revealed by the use of the words 'enervating and artificial,' was simply that the conditions of experiment in LLOYD's laboratory were not representative of the normal fluctuations of laboratory conditions in the locality, nor were they similar to or even comparable with those obtaining at Entebbe. It seemed to me unreasonable to base the far-reaching conclusions reached in LLOYD's summary on evidence of this nature, especially as the conclusions reached in Uganda rested entirely on work done at the ordinary temperatures in a laboratory situated about a quarter of a mile from the lake edge, where the local fly live.

"Dr. TAYLOR's experiments are obviously of quite a different nature, and having during the last year utilised the incubator myself I wish to repudiate his imputation that I have ever regarded this method of experiment as of no significance."

W. Y.

BROWN (A. Forbes). **The Red Cell Adhesion Test in a Case of Trypanosomiasis.**—*Trans. Roy. Soc. Trop. Med. & Hyg.* 1933. Mar. 23. Vol. 26. No. 5. pp. 471–472.

Details are given of a case which was considered on clinical grounds to be one of trypanosomiasis, although daily blood examinations over a period of three weeks were negative. The cerebrospinal fluid contained 240 cells per cmm. ; gland puncture was negative.

A small provocative dose of tryparsamide was given intravenously and the serum sent to Entebbe for the adhesion test, with the following results :—*Trypanosoma gambiense*, strain Brander was 75 per cent. positive ; strain McAlley was 94 per cent. positive ; strain Hamburg was 96 per cent. positive. The patient was then sent to Entebbe and the blood inoculated into a monkey which, in due course, showed *T. gambiense* in its blood. The author concludes as follows :—

"One cannot perhaps insist very strongly on the lessons afforded by a single case. In spite of the failure to demonstrate trypanosomes in the patient's blood by what must be regarded as a very exhaustive examination, the clinical symptoms pointed inexorably to the diagnosis of trypanosomiasis. The red-cell adhesion test supplied invaluable

confirmation of recent infection and led to the appeal to animal inoculation. It would be interesting to learn if other clinicians with more opportunities than the writer have found the test equally useful."

W. Y.

WORMALL (A.). **Some Observations on the Value and the Mechanism of the Red-Cell Adhesion Test for Trypanosomiasis of Man and Other Animals.**—*Parasitology.* 1933. Feb. Vol. 25. No. 1. pp. 64–76. [12 refs.]

The work described in this paper was concerned mainly with attempts (*a*) to reduce and possibly abolish "non-specific" adhesion, (*b*) to increase the percentage of positive results with established cases of trypanosomiasis, and (*c*) to determine whether it would be possible to introduce such modifications as would allow tests to be made with sera which had been collected several days previously.

The following is the summary :—

"1. The results of further tests with the red-cell adhesion phenomenon in trypanosomiasis of man and other animals, described first by Duke & Wallace (1930) and later by Wallace & Wormall (1931), are discussed.

"2. The conclusion is reached that the tests should always be made with several different strains of trypanosomes; in this way the number of negative results with undoubted cases of trypanosomiasis is decreased considerably. It is also advisable to have available stock adhesin sera (human or monkey) so that preliminary tests can be made to determine whether the trypanosomes in any animal are capable of giving adhesion. In doubtful cases of trypanosomiasis, treatment with trypanocidal drugs should be started. This treatment usually results in a marked improvement in the power of the serum or plasma of men and monkeys infected with trypanosomes to give red-cell adhesion.

"3. If a suitable small amount of phenol is added to the serum of a trypanosomiasis patient, this serum can be kept at the ordinary temperatures for 3 weeks or more without appreciable loss of its power to give red-cell adhesion. In this way it is possible to carry out tests at a central laboratory on sera which have been collected at outlying stations.

"4. Experiments have been carried out to determine the amounts of adhesin and complement (or 'X factor') required for red-cell adhesion.

"5. The adhesin is non-dialysable, and in this, and many other respects, it behaves like a true immune body."

W. Y.

DUKE (H. Lyndhurst). **The Domestic Fowl of Uganda as a Host for Trypanosomes of the *Brucei* Group.**—*Parasitology.* 1933. Apr. Vol. 25. No. 2. pp. 171–191. [22 refs.]

These experiments show that the domestic fowl can act as host for trypanosomes of the *brucei* group but not very readily and that in the blood of such birds as become infected trypanosomes are rare. The fowl is unlikely to be a factor in the spread of human trypanosomiasis in nature.

The following summary is given :—

"1. The domestic fowl of Uganda is susceptible to infection with *Trypanosoma rhodesiense* and with *T. brucei* by the bite of *Glossina palpalis* or *G. morsitans*.

"2. A fowl so infected with *T. rhodesiense* can infect clean *G. palpalis* fed upon it, but apparently only with very great difficulty. In theory, therefore, the fowl may play a part in the spread of *Trypanosomiasis rhodesiensis* in nature.

"3. Of 17 fowls bitten by flies carrying heavy gland infections of *T. rhodesiense* only four gave any evidence of infection. In the case of *T. brucei*, 12 fowls were exposed and only one became infected. Two fowls exposed to the Damba trypanosome failed to become infected.

"4. There is some evidence to show that the fowl is only infective to fly in the early stages of its infection, and even then only very slightly. The occurrence of three very slight infections in flies dissected 8 and 10 days after feeding on the infected bird suggests that in the fowl the trypanosome is usually not in a state favourable to development in the tsetse, although it may so develop in an apparently normal manner.

"5. A strain of *T. rhodesiense*, recovered by inoculation into a clean monkey of blood from a fowl experimentally infected by fly-bite, proved in the monkey to be transmissible by tsetse in a perfectly normal manner. Any inhibition of transmissibility exerted by the fowl is therefore temporary and attributable to the influence of the tissues of the bird on the trypanosome.

"6. Of the infected fowls observed in the course of the above experiments only one appeared to be ill. This bird showed unilateral conjunctivitis and general malaise. It was killed some 25 days after its infection, and the inoculation of 10 cc. of its blood infected a clean monkey with *T. rhodesiense* after an incubation period of 6 days. This bird was responsible for one of the two heavy infections found in the 4,339 *G. palpalis* dissected in the course of the above experiments.

"7. That trypanosomes are very rare in the blood of infected fowls is suggested by the failure to infect a clean monkey by the inoculation of 10 cc. of the blood of Fowl 39 a day or two after this bird had caused abortive infections in two clean tsetse. For this reason it is difficult to estimate the susceptibility of the fowl to trypanosomes, as blood inoculation is apparently not an infallible method of demonstrating infection.

"8. From the experiments described in this paper it appears very unlikely that the fowl need be regarded as a factor in the spread of human trypanosomiasis in nature, at all events in *G. palpalis* regions.

"9. There is evidence that the fowl may be more susceptible to infection with *T. rhodesiense* than with *T. brucei*, but only one strain of *T. brucei* was tested. *W. Y.*

Hu (C. H.) & Ch'in (K. Y.). **Development of Lymphocytes and Plasma Cells in Rats Experimentally Infected with Trypanosomiasis.**—*Proc. Soc. Experim. Biol. & Med.* 1933. Jan. Vol. 30. No. 4. pp. 435–436.

In a previous study the authors had found that there was a marked increase of large and medium sized cells with big irregular chromatin masses and abundant basophilic cytoplasm in the spleen and mesenteric and mediastinal lymph nodes of white rats infected with *T. brucei*. These cells, owing to the large numbers of mitotic figures they contained, were considered to be lymphoblasts.

The observations recorded in the present paper were undertaken in order to ascertain why only a certain number of the small lymphoid cells in the lymphoid organs can form large lymphoblasts by hypertrophy, while others remain unchanged. For this purpose, supravital studies were made on the lymphoid organs and blood of a large number of normal and infected animals.

The authors state that "the results indicate: (1) that the small lymphoid cells which can hypertrophy are really the small lymphoblasts, and those which cannot hypertrophy are the intermediate forms and the small lymphocytes; (2) that in the lymphoid organs of the infected animals there is an increase of lymphoblasts having the supravital staining characteristics mentioned in the previous communication; (3) that

mitotic figures are present only in the large and medium-sized cells having the characteristics of lymphoblasts; (4) that plasma cells which are greatly increased in the latter part of infection are derived from lymphoblasts; and (5) that in the blood of the animals at certain stages of infection there was also an increase of the lymphoblasts and occasional presence of plasma cells." *W. Y.*

ZSCHUCKE (Johannes). Erwiderung auf die Arbeit von P. Regendanz: Die experimentelle Erzeugung von Schlafkrankheit beim natürlich immunen Pavian durch Infektion des Liquor cerebrospinalis Archiv für Schiffs- und Tropen-Hygiene, Heft 8, 1932. [**Observations on Regendanz's Experimental Infection of Naturally Immune Baboons by Intrathecal Injection.**]—*Arch. f. Schiffs- u. Trop.-Hyg.* 1933. Apr. Vol. 37. No. 4. pp. 194-196.

REGENDANZ (P.). Antwort auf vorstehende Erwiderung von Dr. Johannes Zschucke auf meine Arbeit: Die experimentelle Erzeugung von Schlafkrankheit beim natürlich immunen Pavian durch Infektion des Liquor cerebrospinalis. [**Rejoinder to Zschucke's Criticism.**]—*Ibid.* pp. 196–198.

Zschucke comments on certain points raised by Regendanz in his recent work on the experimental infection of baboons with sleeping sickness by intrathecal injection (*ante*, p. 117).

He criticizes strongly Regendanz's statement that lumbar puncture should not be made in early cases of sleeping sickness, because of the danger of infecting the cerebrospinal fluid. Zschucke's opinion is that there is very little danger of this, and in any case it is probable that in many patients the central nervous system is infected from the blood at a very early stage of the disease. To exclude lumbar puncture is to exclude one of the most important means of diagnosis.

In the second place Zschucke disputes Regendanz' statement that the nervous symptoms and histological changes in the brain are due to toxins produced by trypanosomes in the cerebrospinal fluid which penetrate the sheaths of the cerebral vessels. Zschucke complains that this appears to be a complicated explanation and that he himself was quite unable to discover any evidence of toxins in the cerebrospinal fluid. He comments on the rarity of trypanosomes in the spinal fluid.

In the third place, Zschucke criticizes Regendanz's statement that human trypanosomiasis would be a harmless disease if the trypanosomes were merely blood parasites.

ii. Regendanz replies at some length to these criticisms. He considers that there is no evidence to support Zschucke's contention that the histological changes in the brain in sleeping sickness patients are regularly the result of blood infection. In his opinion the nervous changes are due to trypanosomes which have penetrated into the cerebrospinal fluid: he draws attention to the fact that in his experiments trypanosomes were never found in the blood of the baboons, and consequently it is unlikely that they reached the circulation from the cerebrospinal fluid.

In reply to Zschucke's second point Regendanz rejoins that toxins have never been demonstrated in the blood, and yet it is commonly held that they are present. He considers his theory is more natural and simpler than one which assumes that the nervous changes are due directly to blood infection. He is not opposed to lumbar puncture on principle, but only against lumbar puncture in the early stage of the disease without specific indications. *W. Y.*

KOFOID (Charles A.) & DONAT (Fae). **Experimental Infection with *Trypanosoma cruzi* from Intestine of Cone-Nose Bug, *Triatoma protracta*.**—*Proc. Soc. Experim. Biol. & Med.* 1933. Jan. Vol. 30. No. 4. pp. 489–491.

—— & ——. **The Experimental Transfer of *Trypanosoma cruzi* from Naturally Infected *Triatoma protracta* to Mammals in California.**—*Bull. Soc. Path. Exot.* 1933. Feb. 8 & 9. Vol. 26. No. 2. pp. 257–259.

In 1916, Kofoid and McCULLOCH described a trypanosome from the digestive tract of the cone-nose bug, *Triatoma protracta*, in California. Although its morphological characters and developmental stages in the bug were indistinguishable from those of *T. cruzi*, the fact that the authors were unable to infect white rats made it impossible to classify the organism definitely as *T. cruzi*, and it was therefore tentatively named *T. triatomae*.

The present papers describe the successful infection of white rats, the Virginia opossum (*Didelphis virginiana*) and the wood rat (*Neotoma fuscipes*). As a result of these observations, it is concluded that *T. triatomae* is identical with *T. cruzi* No human cases of Chagas' disease have so far been recorded in California, but brief illness, and occasionally prolonged illness, has been reported following the bite of the cone-nose bug. *W. Y.*

WHITNALL (A. B. M.). **The Trypanosome Infections of *Glossina pallidipes* in the Umfolosi Game Reserve, Zululand. (Preliminary Report.)**—*Union of South Africa. 18th Report, Director Vet. Services & Animal Industry, Onderstepoort, Pretoria. 1932. Aug.* Pt. I. pp. 21–30. With 1 map & 7 figs.

The following summary is given:—

"The paper gives an account of the trypanosome infections of *G. pallidipes* in Zululand. Attempts have been made to correlate this with game and the nature of the vegetation. Thus it appears that where most game is, the trypanosome infection of tsetse is highest. Where there is water and dense floral growth the percentage of infected flies is higher than where the vegetation is of a more open nature.

"*T. vivax* is the most common trypanosome in the fly, followed by *T. congolense* and then *T. brucei*. It is possible for trypanosomes of the proboscis, gut and salivary gland group to occur in areas where nagana is prevalent, but sleeping sickness does not occur.

"There is a predominance of females caught in the traps at all localities within the Reserve. 30 per cent. to 40 per cent. of the females are in various stages of pregnancy, while 90 per cent. of the males are regarded as 'thin.' Young flies are scarce." *W. Y.*

FINE (J.). **Is Trypanosomiasis in the Lactating Rat Transmitted to the Sucking Young?** [Miscellanea.]—*Ann. Trop. Med. & Parasit.* 1933. Apr. 10. Vol. 27. No. 1. pp. 180–181.

Details are given of a series of experiments indicating that trypanosomiasis in the female rat is not conveyed to the young in the process of lactation. *W. Y.*

MALARIA.

STRICKLAND (C.), ROY (D. N.) & CHAUDHURI (H. P.). **A Year's Observations in Calcutta on the Invasion of the Salivary Glands of *Anopheles stephensi* by Malarial Sporozoites, and the Influence of Some Climatic Conditions.**—*Indian Jl. Med. Res.* 1933. Jan. Vol. 20. No. 3. pp. 819–840. With 3 charts.

The authors found it very easy to infect *A. stephensi* during the cold weather, but almost impossible in the hot weather. This is opposed to BENTLEY'S observations in Bombay, where he found naturally infected mosquitoes most numerous in the hot weather. Sporozoites were found in 9 out of 24 mosquitoes fed on patients with *P. malariae* infections.

The authors used laboratory-bred mosquitoes which were kept in cages in the laboratory. Sixty-two batches were fed during the period January 1931 to February 1932. The shortest interval between feeding and the finding of sporozoites in the glands was 8 days; the longest was 41 days. The rate of gland infection during the period March to July was only 0·74 per cent., but, during the cold weather months, it was 75 per cent. There seems to be a definite check to the invasion of the glands in the hot weather and in the rains. Gland infection was found in 9 of 24 mosquitoes fed on patients with quartan malaria, and the authors consider that if *A. stephensi* is fed on patients with more than 120 gametocytes of any of the three species, during the period of maximal infection, November to January, a 100 per cent. of infections is obtainable. The most favourable temperature for infection lay between 62° and 87°F., or between the means of 71° and 76·5°F. The most favourable relative humidity (mean) was 66 to 70 per cent. The coefficients of correlation between the infection-rates and the physical conditions were worked out by Dr. Chaudhuri; he concludes that *A. stephensi* in Calcutta should not become infected when the relative humidity is above 85 per cent. or below 45 per cent.; or when the temperature is above 95° or below 62°F. *W. Fletcher.*

IYENGAR (M. O. T.). **Experimental Infection of Anopheline Mosquitoes.** —*Indian Jl. Med. Res.* 1933. Jan. Vol. 20. No. 3. pp. 841–861.

The author fed batches of mixed species of anopheles on malaria patients. He gives lists of the species which he successfully infected with subtertian, benign tertian, and quartan respectively.

The following species were found susceptible to experimental infection with *P. falciparum*:—*A. aconitus*, *A. jamesii*, *A. ludlowii*, var. *sundaica*, *A. minimus*, *A. stephensi*, *A. varuna* and, slightly, *A. fuliginosus*. Six species were susceptible to *P. vivax*, namely:—*A. aconitus*, *A. minimus*, *A. stephensi*, *A. varuna*, *A. fuliginosus*, and slightly, *A. hyrcanus*. Four species were susceptible to infection with *P. malariae*, namely:—*A. ludlowii*, *A. stephensi*, *A. culicifacies*, and *A. varuna*. Gland infection was observed in *A. ludlowii* and *A. stephensi*. Gland infections were found in 9 out of 54 *A. stephensi* which had been fed on patients infected with *P. malariae*. The proportion of gametocyte carriers that proved infective was:—*P. falciparum*, 67·6 per cent., *P. vivax* 40·0 per cent., *P. malariae* 21·2 per cent. *W. F.*

HARRISON (C. C.) & RAMSAY (G. C.). **Some Findings and Observations in a Malaria Survey of a Group of Tea Estates in the Eastern Duars District of Northern Bengal and Some Recommendations for the Reduction, Control and Eradication of Malaria in the Area Investigated. A Survey Carried Out under the Auspices of the India Branch, The Ross Institute, London.**—*Jl. Trop. Med. & Hyg.* 1933. Feb. 1. Vol. 36. No. 3. pp. 33–41. With 1 map & 1 chart.

This survey was made over a group of eleven tea estates in the eastern Duars, between October 1931 and September 1932. The results confirm Ramsay's earlier observations (this *Bulletin*, Vol. 27, p. 637, and Vol. 28, p. 579) that *A. minimus* is almost entirely responsible for the malaria of Assam.

It breeds in the clear water at the edges of slow-running streams, until the monsoon comes and makes them muddy, when it migrates to seepages and drains at higher levels. It selects breeding places near to human habitations. The soil of the Duars contains a high percentage of sand; consequently the streams are clear and sparkling. When the ground is disturbed, pools of clear water are often made. Such water is suitable for *A. minimus*, and agricultural operations in the Duars result in malaria, though they would be innocuous in a country where there was colloidal clay. The intense malaria of the Duars is almost entirely man-made and has been created by clearing, draining, pit-digging, and the importation of non-immune labour.

W. F.

RICE (E. Milford) & SAVAGE (J. de la M.). **Malaria Survey of Two Tea Estates in Upper Assam.**—*Records of the Malaria Survey of India.* 1932. Dec. Vol. 3. No. 2. pp. 219–252. With 3 graphs.

In this excellent report the authors show that needless felling of jungle has increased malaria on the two estates in question. They have drawn up a careful balance sheet demonstrating what malaria costs these estates in cash, and what it would be worth their while to pay in order to prevent 25 per cent. of it. Very clear recommendations for control are given.

The two Tea Estates A and B are situated in upper Assam, between 300 and 400 feet above sea level, near a large tributary of the Brahmaputra River; both are areas of hyperendemicity. Subtertian and benign tertian malaria occur in approximately equal proportions, with about 15 per cent. of quartan on estate B. *A. minimus* is the principal carrier: it was found plentiful only during the last three months of the year, and if this finding is substantiated by observations in future years it may mean that control can be limited to the last quarter of the year. Two specimens of *A. philippinensis* were found naturally infected with oöcysts, and this mosquito is possibly a carrier during the earlier months.

There has been a fairly heavy increase of malaria on both estates during the last five years, and this is attributed to jungle felling and the influx of non-immune labour. The drains on estate A were covered with jungle until 1928, the cutting down of this made them suitable breeding places for *A. minimus*, and there was a consequent rise in the malaria rate which is clearly shown in a graph. The same thing

occurred on estate B, where the jungle was cleared in order to prevent Blister Blight, a disease of the tea bush, which is favoured by shade and is also parasitic on rhododendrons. It now appears that it was unnecessary to clear away the vegetation over the streams, because it neither shaded the tea bushes nor consisted of rhododendrons.

The authors have made out a balance sheet showing the number of deaths and days of work lost from malaria, and giving the value of these in money, taking the figure of £30 as the value of a coolie and the average value of his work as about 2s. 6d. a day. The annual loss on estate A worked out at £2,715. Adopting the "eight years purchase of profit valuation" they calculate that the capitalized value of the loss, due to malaria, is £2,715 × 8 = £21,720. "Aiming at a 50 per cent. reduction in the malaria incidence, and being confident of a minimum of 25 per cent. reduction, we take the latter figure as a definite goal, thereby reducing the capitalized value of malaria for our present purpose to £5,430. We now suggest that the interest on this sum at 5 per cent., or £272, is the amount which can justifiably be expended per annum on reducing the incidence of malaria on Estate A." This estate comprises 714 acres, is valued at £53,550, and employs about 1,000 coolies. In the same way it was calculated that Estate B should spend £150.

The authors' recommendations come well within these figures. On Estate A they found that the only breeding place of *A. minimus* was the main estate drain, and they recommend that this should be oiled by anchoring bags of cotton waste, soaked in waste oil from the estate factory, on each side of the drain at intervals of 100 yards, and renewing them once a week. On Estate B anopheline breeding takes place in many places, and they do not consider that any expenditure for anti-mosquito measures should be made at present, as jungle will cover most of the areas if allowed to grow; they suggest in the meantime that the children and carriers should be treated with plasmoquinine in order to destroy gametocytes. *W. F.*

COVELL (G.) & BAILY (J. D.). **The Study of a Regional Epidemic of Malaria in Northern Sind.**—*Records of the Malaria Survey of India.* 1932. Dec. Vol. 3. No. 2. pp. 279–322. With 1 map, 1 plan & 13 graphs. [36 refs.]

An epidemic of malaria occurred in Northern Sind in the autumn of 1929; the precipitating cause was excessive rainfall, with flooding and an abnormally high relative humidity, following several abnormally dry years.

There had been no big epidemic for 12 years, and the results of spleen examinations showed that immunity was low. The spleen rate rose to 80 in the year after the epidemic. The prevalence of *A. culicifacies* was very high at the beginning of the outbreak, but few hatched out after the first 3 or 4 weeks. The sporozoite rate reached 30 per cent. at one period. Very few crescent carriers were found at the beginning of this epidemic, and it is difficult to see how infection spread, unless the anopheles had a very wide dispersion after feeding. The same phenomenon has puzzled other observers in other epidemics. The crescent rate rose rapidly and reached a high figure about 2 or 3 weeks after the epidemic had reached its highest peak; *i.e.*, about the 9th week. *W. F.*

ABRAHAM (A. C.). **The Anopheline Mosquitoes of Hyderabad, Deccan, and their Control.**—*Records of the Malaria Survey of India.* 1932. Dec. Vol. 3. No. 2. pp. 179–195. With 1 map & 2 graphs.

Contains an interesting note on the water-hyacinth.

Hyderabad city comprises the ancient walled town south of the Musi River, and the more modern Chaderghat on the North. Within the walled city, there are more than 6,000 wells; *A. stephensi* is plentiful and 3·5 per cent. are infected; the spleen rate is 50 per cent. In Chaderghat, the spleen rate is only 10 to 25 per cent., and the carriers are probably *A. aconitus* and *A. culicifacies* which breed in the Musi River, on account of (*a*) innumerable pits and pools produced by excavation of sand from the river bed, and (*b*) the profuse growth of water-hyacinth. The water-hyacinth (*Eichornia crassipes*), a native of Brazil, has now become a pest in many countries into which it has been introduced. It can propagate itself by seeds, suckers, and lateral branches. It has been suggested that it would cover water so completely as to be useful in malaria control, but in Hyderabad it shelters larvae and mechanically interferes with the action of larvicides. Removal of the plant by hand is the method adopted. It is useful as fodder for cattle, as manure, as a source of potassium chloride, for the manufacture of paper, and for the preparation of ink from its flowers.

W. F.

VAUCEL (M.) & SALEUN (G.). Le paludisme à Brazzaville. [**Malaria at Brazzaville.**]—*Bull. Soc. Path. Exot.* 1933. Jan. 11. Vol. 26. No. 1. pp. 18–23.

There has been an alarming increase, during the last two years, in the amount of malaria at Brazzaville, where it was formerly uncommon and where less than a dozen of the 600 Europeans suffered from fever during the year. The parasite index in native children was 26 per cent. in 1927, but now it is 93. *P. malariae* is the commonest parasite in the rains, and *P. falciparum* in the dry weather; *P. vivax* is not very rare. The common anopheline is *A. costalis.* *W. F.*

SICART (Marcel) & VILLAIN (Georges). Contribution à l'étude du paludisme dans le Cap Bon. [**Malaria in Cap Bon.**]—*Tunisie Méd.* 1932. Nov. Vol. 26. No. 9. pp. 429–446. With 6 figs. (1 map).

Cap Bon, the southern boundary of the Gulf of Tunis, is highly malarious. Quartan is the commonest fever in the northern and eastern parts of the peninsula, but, for some unexplained reason, it is much less common in the south and west. Money is not available for extensive drainage works. *W. F.*

GALLIARD (Henri). Culicidès du Gabon. IV. Essai sur leur biologie dans ses rapports avec le paludisme local. [**The Culicidae of the Gabon and their Relation to Malaria.**]—*Ann. Parasit. Humaine et Comparée.* 1932. Nov. 1. Vol. 10. No. 6. pp. 465–493. With 16 figs. on 8 plates & 1 map. [59 refs.]

These observations were made in the western Gabon, just south of the equator; except for a little grass land, the country is mountainous

and covered with jungle. There is a dry season from June to September. The parasite index at the end of the rains was about 65 per cent. in children under 10 years of age and 8 per cent. in adults; in the dry season these figures were approximately halved. *P. malariae* accounted for 2 per cent. of the infections, the rest were due to *P. falciparum*. Seven species of anophelines, and 35 species of culicines were identified. The most numerous anophelines were *A. mauritianus*, *A. funestus* and *A. costalis*. The first was the most common, and was ubiquitous; it breeds in any water, running or stagnant, clear or weedy, exposed or shaded. *A. funestus* was found in the grass lands, and *A. costalis* on the coast. Mosquitoes were most common in houses at the end of the rains; none were caught during the dry season.

W. F.

MORIN (H. G. S.) & TOUMANOFF (C.). Sur le rôle de *Anopheles maculatus* dans la transmission du paludisme au Tonkin. [**The Rôle of *A. maculatus* as a Transmitter of Malaria in Tonking.**]—*Bull. Soc. Path. Exot.* 1933. Jan. 11. Vol. 26. No. 1. pp. 83–92. With 1 fig.

It is impossible, owing to the difficulty of catching adults, to say definitely whether this mosquito is an important carrier of malaria in Tonking.

Two naturally infected specimens have been found among 45 examined in that area of Tonking which is known as the zone of intermediate altitude. This mosquito does not stay in houses during the day and it is therefore difficult to catch wild adults. The larvae are common in many places where malaria is prevalent, but they are also found in parts of the highlands where there is none. Local conditions which favour or hinder the contact of this mosquito with man may make it a carrier in one district, and harmless in another. Attention is drawn to the importance of day shelters for mosquitoes such as drains, ditches, banks, and bamboos in the neighbourhood of houses. *W. F.*

RUSSELL (Paul F.). **Malaria in the Philippine Islands.**—*Amer. Jl. Trop. Med.* 1933. Mar. Vol. 13. No. 2. pp. 167–178. [2 refs.]

HOLT (Rufus L.) & RUSSELL (Paul F.). **Malaria and Anopheles Reconnaissance in the Philippines.**—*Philippine Jl. Sci.* 1932. Nov. Vol. 49. No. 3. pp. 305–371. With 1 fig. & 7 plates (3 maps). [60 refs.]

Thorough malaria-control by any of the approved methods is beyond the means of the Philippines. All the available methods should be employed as means permit, and, in time, there may be gradual improvement.

Malaria investigation is jointly supported by the Bureau of Science, Manila, and the Rockefeller Foundation. Dr. Russell considers that malaria is a disease of great, but not paramount, importance in the Philippines. There is no malaria on flat land, but it occurs where there is a change of altitude; there are thus two malarial zones, one where the coastal plain passes into the intermediate plateau, and another where the plateau rises into the foothills of the mountains. The coastal plain is non-malarious because it is flat; where hills rise gradually from it, it is malarious. There is no malaria above 2,000 feet. The disease

varies with the seasons : when there is no rain, or when there is much, there is little malaria. " Transition seasons, between wet and dry and vice versa, like transition regions from lower to higher altitudes, are apt to be malarious in the Philippines." The carriers are the *funestus-minimus* sub-group. MANALANG'S " *A. funestus* is chiefly *A. minimus* var. *flavirostris,* but may sometimes include *A. mangyanus.*" These mosquitoes breed among the bank-side vegetation of clear, gently-running streams, slightly shaded, in foothill areas. The salt water anopheline of the coasts (*A. litoralis,* King 1932. The salt-water *ludlowi* of earlier writers) though akin to the *ludlowi* of Malaya, does not carry malaria.

Paris green control, continuously applied, has been found relatively economical and effective. It is of proved value where people are concentrated in limited areas such as camps and the like, but for general application the cost is more than the people can afford. " It cannot be said that there has ever been demonstrated in the Islands a malarial-control project for typical small communities which was within the means of the people." Quinine and quinoplasmine will never control malaria ; it is impossible to get a large group of civilians to take antimalarial drugs systematically, but they are adjuvants of value ; there is no evidence that malaria control will ever be achieved in the Philippines without anti-larval measures. Not one but all available weapons must be utilized, and in time the incidence of malaria-carrying mosquitoes should be reduced. There is no more permanence in sight for malaria control than for road repairs. In the Tropics, at least, it must be carried out year by year during this century, and the next. " The tropics are generally poor in *money,* but rich in *time.*"

W. F.

SOESILO (R.). Enkele grepen uit de malaria epidemiologie. [**Selections from the Epidemiology of Malaria.**]—*Geneesk. Tijdschr. v. Nederl.-Indië.* 1933. Jan. 17. Vol. 73. No. 2. pp. 67–74.

In this lecture the author deals with a number of practical points in epidemiological analysis and practice. Some of these may be noticed here.

The number of species of anophelines in the Dutch East Indies is about 46, but malaria-carrying mosquitoes are about 1-10th of this number. Moreover, the majority of these show very definite preferences for certain breeding places. In this way the task of malaria prevention by anti-larval measures is brought within compass by attention only to particular areas and particular species. In Batavia, for example, only the fishponds, in which the brackish-water *A. ludlowi* breeds, require treatment.

A characteristic of hyperendemic malaria is a high spleen index with a maximum (80–90 per cent.) reached at 2 years of age and persistence at that level. The parasite index is lower than the spleen index and is higher in children than in adults. Another characteristic of endemicity is that the percentage of gamete carriers is small. An example of these findings may be extracted from tables referring to chronically endemic areas of the island of Nias. Ninety-three children examined gave a parasite index of 50·5 per cent., a spleen index of 92·5 per cent. and 3 gamete carriers. The corresponding figures for 126 adults were 20·3, 90·5 and 0. The picture is quite another in a population previously free from malaria and in the grip of an epidemic. Here the parasite

index is at first higher than the spleen index and just about equal in children and adults, while the gamete carriers are both numerous and not less in adults than in children. Absence of large spleens also points to fresh malarial incidence.

A permanently high spleen index among the adults living in a chronically malarial region is regarded as indication of the continued and efficacious parasiticide action of that organ, whilst the small number of parasite carriers is ascribed to the development of an immunity. These are not to be regarded as facts of necessarily universal application throughout all the world. *W. F. Harvey.*

JOURNAL OF THE PUBLIC HEALTH ASSOCIATION OF JAPAN. 1933. Feb. Vol. 9. No. 2. pp. 1–5.—**Malaria and its Prevention in Japan.**

Malaria is not a common disease in Japan proper. Its occurrence is limited to the summer, and it never appears in epidemic form. It is always of the benign tertian type, except in the Okinawa Islands where subtertian occurs. Quartan malaria does not exist. In Formosa, malaria is decreasing, but it is still one of the most important problems in public health, and malaria cases constitute more than 10 per cent. of all the patients treated at government institutions. In Korea, malaria is more prevalent than in Japan ; during 1931, there were 1,583 deaths from it in a population of 21 millions. In the Kwantung Territory and the South Manchuria Railway Zones, the disease increases year by year. *W. F.*

GIGLIOLI (G.). **Some Statistical Data on the Incidence of the Various Malarial Parasites in the River Areas of the Interior.**—*Brit. Guiana Med. Ann. for 1932.* pp. 98–102.

Benign tertian is the most prevalent form in the river areas of the interior of British Guiana. It accounted for 81·4 per cent. of 1,247 cases of malaria examined at the Mackenzie Hospital. Subtertian was 15·7 per cent., and quartan 2·9 per cent. In reality, quartan is more common than this figure suggests ; it is so mild that few cases come to hospital for treatment. The benign tertian season is from July to November ; the subtertian season is in September ; the quartan from October to May. *W. F.*

BOYD (Mark F.) & PONTON (Gerald). **The Recent Distribution of Malaria in the South-eastern United States.**—*Amer. Jl. Trop. Med.* 1933. Mar. Vol. 13. No. 2. pp. 143–166. With 24 figs.

The distribution of malaria is correlated with the geology of the country. It is endemic in areas of "solution topography." The variations of intensity from year to year, within these areas, are correlated with the rainfall.

The distribution of malaria in this region is not related to its fluvial hydrography : the malarial zone bisects the river basins considerably above their points of discharge, but it coincides with the areas of "solution topography." These are areas underlain by soluble limestone which is gradually dissolved, in places, by the action of water, and as the result of this, extensive underground passages are formed, some of

which contain underground rivers while others become dry caverns. Here and there the roof of a subterranean passage gives way, forming a steep-walled, funnel-shaped depression of relatively small diameter, which is known as a "sink" or "sink-hole." At first, these depressions may have a pool of water at the bottom, or a stream appearing at one side and disappearing underground again at the other. Gradually the sink becomes filled in, leaving a basin-shaped depression. These depressions which vary in size from a few hundred feet to several miles in diameter represent the last stages of solution erosion. Some are permanently filled with water, forming ponds or lakes, some remain dry except during heavy rain, in others an underground stream comes to the surface. In such country, there are no superficial erosion channels or river beds to run off the surface water, and in wet summers this collects in the numerous shallow, basin-shaped depressions devoid of outlet. This promotes the breeding of *A. quadrimaculatus*, and intensifies malaria. The water in the lime-sinks, in the sluggish streams flowing from some of them, and in many of the basins temporarily filled with water in wet seasons is alkaline. Such water is favoured by *A. quadrimaculatus*; but in the sandy, flat woods where the smaller depressions are filled with vegetation the water is acid, and there *A. crucians* breeds. *W. F.*

BOGOJAWLENSKI (N. A.). Die Malaria im Distrikt Kasach (Aserbajdschan) nach langjährigen Beobachtungen. [**Malaria in Kasach District, Azerbaijan.**]—*Arch. f. Schiffs- u. Trop.-Hyg.* 1933. Jan. Vol. 37. No. 1. pp. 19–28. With 5 figs.

The work was done in the district of Kasach situated in the extreme north-western portion of the Soviet Republic of Azerbaijan. The population of 121,255 is chiefly rural, being distributed in 279 villages. The author describes the physical and economic conditions of the district. The important vectors of malaria are *Anopheles maculipennis* and *A. superpictus*. Whilst the breeding places of the former are ubiquitous, the latter is much more selective, having a strong preference for puddles in river beds. Both are equally zoophilic. There are grounds for believing that *Anopheles superpictus* is actively migratory up to 8 kilometres. For hibernation they select horse stables, which are warm and they get the blood required from the horses and other animals. The material for estimating the distribution of malaria in the districts was obtained from the results of the research expedition (10,712 persons) and the results of previous inspections (21,985 persons). The spleen, Ross and parasite indices were :—63·9 : 3·3 : 29·8 per cent. respectively. As regards the parasites the frequency was :—*P. malariae* 37·3 per cent., *P. vivax* 26·3 per cent., *P. falciparum* 24·7 per cent., undetermined species 9·2 per cent., mixed infections 2·5 per cent. In young children cerebral malaria was not uncommon. There are two peaks of malaria in Kasach, a small one April to May, probably relapse cases, and a second higher one in autumn, nearly all being primary infections. As regards the antimalarial measures, they commenced very simply, with therapeutic and prophylactic administration of quinine, and have gradually expanded to the other methods usually employed. For the special problem of the district, namely, the destruction of mosquitoes in the stables, they employed smoke, especially tobacco smoke, and in 1930 1,010 kg. of tobacco were used for the purpose. *E. D. W. Greig.*

PERALVO CABALLERO (Antonio). [Servicio Sanitario Profilaxis Antipalúdica]. Pantano del Guadalmellato. Junta Social. [**The Guadalmellato Swamp.**]—61 pp. With 17 figs. on 9 plates & 1 coloured folding map. 1930. Nov. Publicaciones de la Confederación Sindical Hidrográfica del Guadalquivir.

This brochure, published by the Guadalquivir Hydrographic Syndicate, contains a report of the bonification of the Guadalmellato swamp and its drainage, illustrated by self-explanatory photographs. The work was carried on during the six years, 1925–30 inclusive. All the labourers were given quinine, in doses varying from 0·5 to 1 gm. on two or four successive days, for adult males, women and children being given proportionately less. In 1925 there were 270 persons and 15 of them developed malaria, *i.e.*, 5·5 per cent.; in 1926 there were 61 infected among 300 (20·6 per cent.); in 1927, 17 among 470 (3·6); in 1928 there were 1,040 with less than a month's preventive treatment and 972 was the average during 5 months. Among the latter there were 17 cases or 1·7 per cent. infected. In 1929 26 cases among 1,309 (1·9), and in 1930, when the work was being completed, three cases among 310 (1·1 per cent.). Small individual estates are also described separately. Illustrations show the construction of canals, dams, bridges, etc., erected during the course of the work. *H. H. S.*

RAGAZZI (Giorgio). La malaria a Tauorga. [**Malaria in Tauorga (Tripolitania).**]—*Arch. Ital. Sci. Med. Colon.* 1933. Apr. 1. Vol. 14. No. 4. pp. 264–276. With 8 figs. English summary (7 lines).

The author describes the oasis of Tauorga and photographs show well the nature of the terrain. The population of the district is 3,190 and he examined rather more than one-third, 1,106. Among these he found 71 with *P. falciparum* in their blood (no other form of the parasite was seen), and 450 had enlarged spleen, an index of 40·7 per cent. Twelve per cent. of 500 specimens of mosquitoes caught in the market place were *A. mauritianus.* *H. H. S.*

DAVEY (T. H.) & GORDON (R. M.). **The Estimation of the Density of Infective Anophelines as a Method of Calculating the Relative Risk of Inoculation with Malaria from Different Species or in Different Localities.**—*Ann. Trop. Med. & Parasit.* 1933. Apr. 10. Vol. 27. No. 1. pp. 27–52. With 2 graphs.

The Anopheline Density is estimated by the following formula:

$$\frac{\text{Number of female anophelines captured} + x}{\text{Number of rooms examined}}$$

The figure thus obtained represents the average number of female anophelines found at the time of examination of the house, in the early mornings. The term x is "a previously estimated amount representing the number of anophelines which had left the houses before the time of their examination." In West Africa, where *A. costalis* and *A. funestus* are the carriers, few leave the house before dawn and x may be neglected.

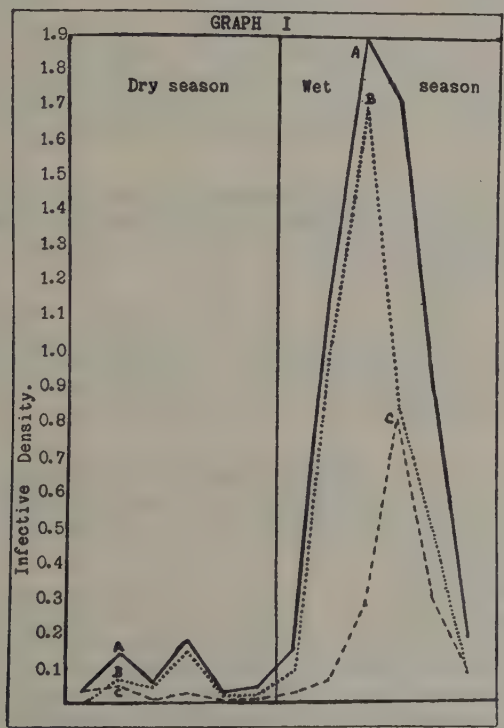
Since it is often impossible to dissect all the mosquitoes captured, the Anopheline Infective Ratio is estimated from the formula:

$$\frac{\text{Number of sporozoite infected anophelines}}{\text{Number of female anophelines dissected}}$$

The Infective Density, which is the average number of infective anophelines per room per day, is obtained by multiplying the Anopheline Density by the Anopheline Infective Ratio, thus :

$$\frac{\text{Number of female anophelines} + x}{\text{Number of rooms}} \times \frac{\text{Number of sporozoite infections}}{\text{Number dissected}}$$

The Infective Density is of considerable practical value, for example in cases where a medical officer has to choose between two sites for occupation by troops. Again, by its means the progress effected by antimalaria measures may be charted, and it allows an estimation to be made of the relative importance of different species of anopheles as carriers of malaria.



Showing the seasonal variation in anopheline infective density for all species at Kissy (A), and the parts played in determining it by *A. costalis* (B), and *A. funestus* (C).

The striking difference between infective densities in the wet and dry season is brought out, also the predominant part played by *A. costalis* in maintaining the infective density throughout the year.

[Reproduced from the *Annals of Tropical Medicine and Parasitology*.]

The Infective Density was estimated in Freetown, where anti-mosquito measures have been in force over a long period, and, by way of comparison, in the neighbouring unsanitated village of Kissy. In Freetown it was 0·024, while in Kissy it was 0·844, or 34 times greater. The human malaria rates, however, did not show the same difference ; 81 per cent. of the school children in Freetown were infected, as compared with 92 per cent. in Kissy. " With our present lack of knowledge regarding the duration of the primary attacks and the number and

duration of the subsequent relapses, the estimation of the malaria incidence in the general population is of little value as an indication of the malaria inoculation risk in a community. . . . To ascertain what correlation exists between the anopheline infective density and the human malaria rate, we must conduct our investigations amongst that section of the population that is exposed to infection for the first time ; that is to say, the non-immune newcomer to the district, or else the infant population during the first few months of life." The examination of infants under 3 months of age at Kissy, with an Infective Density of 1·29, showed that 52 per cent. were infected ; but at Freetown, where the Infective Density was 0·031, only 5 per cent. were infected. With each few months of advancing age, the original difference steadily diminishes. " It is only a postponement of the disease ; . . . as the child grows older parasites are to be found in its blood almost continuously, so that during these later years it is little better off than if it had lived in an unsanitated village. Whatever different views are held regarding the effect of anti-anopheline measures on the health of the native community, no such difference of opinion can exist regarding its value in preserving the health of the European." *W. F.*

ANDERSON (Drysdale). **Notes on Mosquito-borne Diseases in Southern Nigeria : IV. The Sex Ratio of House-Haunting Mosquitoes.**—*Jl. Trop. Med. & Hyg.* 1932. Nov. 15. Vol. 35. No. 22. pp. 340–343. With 4 graphs.

The author noted in the daily adult mosquito catches at Abeokuta and Onitsha, in Nigeria, that there was a considerable variation in the proportion of the two sexes according to the season and the species. He concludes that the sex ratio in the house catches is not fortuitous but is dependent upon the bionomics of the species. *W. F.*

ANDERSON (Drysdale). **Notes on Mosquito-borne Diseases in Southern Nigeria : V. The Spleen-Rate as an Index to Malarial Intensity.**—*Jl. Trop. Med. & Hyg.* 1933. Apr. 1. Vol. 36. No. 7. pp. 97–98. With 2 graphs.

The seasonal variation of the spleen rate gives only a gross indication as to the presence of malaria. In Boyd's method, the enlarged spleens are classified as 1, 2, 3, or 4 according to their size. The total of the spleens in each category is multiplied by the number of the category ; and the four products are then added together giving what is known as the " weighted total." For example, if there were 5 enlarged spleens in each class, the weighted total would be $(5\times1)+(5\times2)+(5\times3)+(5\times4)=50$. The weighted total gives more accurate information than the simple spleen rate ; but it is not entirely satisfactory because the spleens in class 2 are not twice the size of those in class 1, nor are those in class 4 twice the size of those in class 2. For scientific accuracy it is necessary to know the relation of the surface markings to the actual weight of the spleen. *W. F.*

KLIGLER (I. J.), MER (G.) & OLITZKI (L.). **Studies on Malaria. XI. Seasonal Variations in the Food Preference of *Anopheles elutus*.**—*Trans. Roy. Soc. Trop. Med. & Hyg.* 1932. Nov. 30. Vol. 26. No. 3. pp. 283–287.

Specimens of *A. elutus* were collected from houses and stables in the two settlements Yessod and Mellaha. The ingested blood was

expressed on to filter paper and sent to the laboratory at Jerusalem for precipitin tests. The percentage of human blood was highest in May, June and November. There was a constant low incidence in April and early May which points to the possibility that, in colder climates, the feeding habits of anopheles differ from those in warmer ones. Climatic factors may account for the predominance of zoophilic races. *W. F.*

SCHWETZ (J.). Sur la répartition de trois espèces malariennes, suivant l'âge, chez les indigènes de l'Afrique équatoriale et centrale. [**The Species of Malaria Parasites Present at Different Ages in Natives of Central Africa.**]—*C. R. Soc. Biol.* 1932. Vol. 111. No. 40. pp. 1097–1099.

The intensity of infection diminishes with age. In infants, parasites are numerous ; in adults it is necessary to examine thick films in order to find any. Crescents are present in 50 per cent. of the infants, but are absent in adults. *P. malariae* is nearly as common as *P. falciparum* in infants, but after the age of 10 it is very rare. *P. vivax* is present in 5 per cent. or more of infants, but hardly ever in children over 3. (See SCHWETZ, below.) *W. F.*

SCHWETZ (J.). Le "mystère" de la fièvre quarte et de la tierce bénigne en Afrique Equatoriale et Centrale. [**The "Mystery" of Quartan and Benign Tertian Malaria in Equatorial and Central Africa.**]—*Bull. Soc. Path. Exot.* 1932. Dec. 14. Vol. 25. No. 10. pp. 1062–1074.

Referring to a paper by Professor MARCHOUX, "*La fièvre quarte et son mystère,*" the author states that, judging from his own experience in Africa, there is no more mystery attached to quartan than to benign tertian.

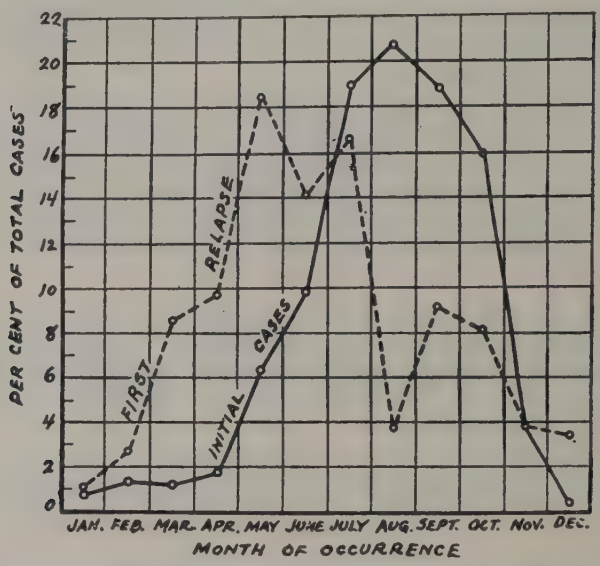
MARCHOUX pointed out that quartan differed from the other two forms of malaria in its more rapid disappearance from European countries ; its peculiar localization ; its presence in winter when mosquitoes are rare ; its frequence in Africans in certain parts of West Africa, while it seldom attacks Europeans living in the same places ; and he suggested that it might have an intermediate host other than the mosquito. The author, working at Stanleyville, has found benign tertian and quartan rare, both in native children and in Europeans. Benign tertian is even rarer than quartan, and he asks why this should be so. He suggests that it may be because the local carriers *A. costalis, A. funestus, A. marshalli* and *A. nili* are not so readily infected by *P. malariae* and *P. vivax* as by *P. falciparum.* He has noted that, as children grow older, *P. malariae* infections disappear earlier than those due to *P. falciparum*, and that *P. vivax* infections disappear still earlier, yet he has found *P. vivax* infections more resistant to quinine than infections with the other types. *W. F.*

GORDON (R. M.) & DAVEY (T. H.). **A Further Note on the Increase of *P. malariae* in Freetown, Sierra Leone.**—*Ann. Trop. Med. & Parasit.* 1933. Apr. 10. Vol. 27. No. 1. pp. 53–55.

Quartan malaria is definitely established in Freetown and is becoming the predominant type among children. In children 3 to 14 years old, belonging to the native village of Kissy, 20 per cent. of the infections were *P. falciparum*, 41 per cent. *P. malariae*, 28 per cent. a mixture of the two, and 6 per cent. *P. vivax*. *W. F.*

BORDEN (William B.). **A Study of Malarial Relapses in the United States Army.**—*Amer. Jl. Hyg.* 1933. Jan. Vol. 17. No. 1. pp. 1–36. With 4 figs. [19 refs.]

A rise in the malaria admissions occurs in the spring before infected mosquitoes are to be found. It is concluded that this rise is due to latent infections and late relapses.



The occurrence of initial cases and first relapses of tertian malaria in the United States by months, showing that the maximum occurrence of first relapses is in May and of initial cases in August.

[Reproduced from the *American Journal of Hygiene*.]

The record of each man in the United States army who had suffered from malaria during the years 1922–1929 was scrutinized in order to determine if there was a seasonal variation in the occurrence of relapses. It was found that there were many readmissions and primary cases in the spring, though no infected mosquitoes are found before the second half of June. The primary cases occurring at this season must have been due to latent infections contracted during the summer and autumn of the previous year. The highest number of first relapses occurred in May, nine months after the highest number of primary cases in the previous year.

In benign tertian : after a first attack, 23·3 per cent. relapsed ; after a first relapse, 25 per cent. relapsed ; after a second relapse, 20·9 per cent. ; after a third relapse, 22·2 per cent. [Which accords with the old rule that a quarter of the cases relapse after treatment with quinine at the primary attack, or at any subsequent relapse]. The relapse rate for primary cases of subtertian malaria was 17·9 per cent. There were no second relapses. Cases which received four or five weeks' treatment at the outset relapsed less than cases which received only three. *W. F.*

BOYD (Mark F.) & STRATMAN-THOMAS (Warren K.). **Studies on Benign Tertian Malaria. I. On the Occurrence of Acquired Tolerance to** *Plasmodium vivax.*—*Amer. Jl. Hyg.* 1933. Jan. Vol. 17. No. 1. pp. 55–59.

The authors' experiments corroborate the observation that infection with a given strain of benign tertian produces a tolerance to that strain, but not to other strains.

In the first experiment, two patients were bitten by mosquitoes infected with the McCoy strain of benign tertian, and both developed malaria. The attacks terminated spontaneously, and, two or three months later, they were again bitten by mosquitoes infected with the McCoy strain. Neither of them became infected, though sporozoites were present in the mosquitoes' glands and controls were infected. Parasites were still present in the blood of the two patients at the time of the second biting. In the second experiment, two patients were bitten by mosquitoes infected with the Vanse and the Cabler strains, respectively. After recovery, which was assisted by quinine, they were bitten again ; this time, by mosquitoes infected with the McCoy strain. They both became infected. Neither of the patients in the second experiment had parasites in his peripheral blood at the time of the second biting. [Therefore the conditions of the two experiments were not quite the same.] *W. F.*

BOYD (Mark F.) & STRATMAN-THOMAS (Warren K.). **Studies on** *Plasmodium vivax.* **1. The Microgametocytes as a Factor in the Infectiousness of the Infected Human.**—*Amer. Jl. Hyg.* 1932. Nov. Vol. 16. No. 3. pp. 845–850.

——. **2. The Influence of Temperature on the Duration of the Extrinsic Incubation Period.**—*Ibid.* pp. 851–853. With 1 chart.

During 1931, the authors examined 849 *A. quadrimaculatus* that had taken an infecting meal. Of these, 47·4 per cent. were found to be infected with *P. vivax.* They found that there were refractory individuals in every batch, and that this was not overcome by repeatedly feeding the mosquitoes on a patient. The proportion of mosquitoes becoming infected was not attributable to the number of gametocytes in the patient's blood, but the number of oöcysts in the stomachs of the mosquitoes which actually became infected was directly dependent on the number of microgametocytes.

Batches of *A. quadrimaculatus* incubating an infection of *P. vivax* were kept in cool incubators and each day those that died were dissected. The extrinsic incubation period was taken to be complete when sporozoites were first found in the salivary glands. The shortest incubation took place between the mean temperatures of 24·2° and 25·4°C., and occupied 11 days. Higher minimum temperatures were fatal to the mosquitoes. Between 19·3° and 21·6°C. the incubation was lengthened to 21 days. These circumstances would limit the transmission of *P. vivax* by *A. quadrimaculatus* during the extreme heat of midsummer. *W. F.*

CARLEY (Paul S.). **The Influence of Race in Malarial Splenomegaly in Panama.**—*Amer. Jl. Trop. Med.* 1932. Nov. Vol. 12. No. 6. pp. 467–471.

Splenomegaly, as a sign of malaria, is more constant in the mestizo than in the negro. A group of Panamanian children comprising 598

negroes and 493 mestizos was examined. One-third of the cases of malaria in the negroes and one-fourth of the cases in mestizos had parasites without splenomegaly. Mestizos are persons of mixed white, Indian and negro blood, in whom white predominates. *W. F.*

ARCHIVES DE L'INSTITUT PASTEUR D'ALGÉRIE. 1932. Dec. Vol. 10. No. 4. pp. 485–601. With 16 figs.—Cours de paludologie de l'Institut Pasteur d'Algérie, 1932 (Sommaires). [**The Malariology Course at the Pasteur Institute of Algeria.**] [SERGENT (Edm.) et al.]

This is a collection of the excellent summaries which are handed to the students at the beginning of each lecture, or laboratory class.

The malaria course at the Institut Pasteur d'Algérie occupies 40 days and comprises 18 lectures followed by practical work in the laboratory, 6 demonstrations in the field, and two malaria surveys to be made by the student himself. Among the lecturers are MM. Edm. and Et. SERGENT, BÉQUET, DONATIEN, CATANEI, SENEVET, PARROT, BENHAMOU, FOLEY, and BALENSI. *W. F.*

RECORDS OF THE MALARIA SURVEY OF INDIA. 1932. Dec. Vol. 3. No. 2. pp. 269–270.—**Principles to be observed in the Preparation of Canal Projects and in their Execution.**

All channels, where possible, should be aligned along water sheds. The importance of providing for drainage should be borne in mind. The full supply of water should be as little as possible above the level of the adjoining land. Where canals cross natural drainage, arrangements should be made to pass storm water under or into the canal. No weirs should be constructed on rivers near towns, unless suitable provision is made to prevent water-logging. Borrow-pits, when they are necessary, should be dug in the canal bed. Main canals and branches should not be taken within 2 miles of an existing town, nor should new towns be built within 3 miles of them. Canal irrigation should not be permitted in areas likely to become water-logged, nor where the rise of the water table would be accompanied by the spread of alkali. *W. F.*

MEDICAL PARASITOLOGY AND PARASITIC DISEASES. Moscow. 1932. Vol. 1. No. 2. pp. 65–116. [In Russian.]—**First U.S.S.R. Conference on the Use of Aeroplanes in the Control of Malaria.**

An account of the proceedings of a conference on the use of aeroplanes in antimosquito work, held in Moscow, November, 1931. The method of dusting mosquito-breeding places with Paris green from aeroplanes was first introduced in Russia in 1929, when 100 hectares were treated by this method. By 1931 this area was increased to 110,000 hectares. The papers read at the conference are devoted to questions of organization, technique and propaganda of the method, as well as to the results obtained in various parts of the country. The results appear to be so promising that it is intended to employ aeroplanes for mosquito-control on a much larger scale. *C. A. Hoare.*

LE FORZE SANITARIE. 1933. Jan. 10–20. Vol. 2. No. 1–2. pp. 1–132. With illustrations.—Numero doppio dedicato a "Littoria" ed alla bonifica dell' Agro Pontino. [**Bonification in Agro Pontino.**]

The first half of this double number is devoted to malaria in general and the measures of bonification undertaken in Agro Pontino in particular. The whole is illustrated by a beautifully reproduced plate of "Littoria" showing a bird's-eye view of the district in its improved, in fact renovated, state.

There is an introductory article on this area of the Agro Romano, followed by general remarks on the measures taken in hand since 1926. Succeeding articles are contributed by men whose names are household words in the world of malaria investigation.

Professor MARCHIAFAVA writes on the different parasites, their effects and the symptoms to which they give rise and he includes statistics on the mortality from this cause from 1887–1930 in Italy as a whole and by districts. Professor BASTIANELLI writes on the life-cycle of the plasmodium and on the treatment of malaria, while Professor MISSIROLI discusses the possibility of eradication.

A concluding section on the liberation of Agro Romano from the pestilence has already been reviewed [see below, p. 498]. The whole forms a very interesting and informative report. *H. H. S.*

DE LUCA (Benedetto). Sopra alcuni più recenti metodi di slatentizzazione della malaria. (**On Most Recent Methods of Reactivation of Malaria.**)—*Riv. di Malariologia.* 1932. May-June. Vol. 11. No. 3. pp. 301–307. English summary (7 lines) p. 413.

The author gives details of 20 cases of malaria, in ten of whom he tested the value of injecting 0·5 mgm. tuberculin to unmask a latent infection (Boeri's method) and in the other ten a series of injections, up to 6, of 10 cc. of a 10 per cent. solution of $CaCl_2$ intravenously (Monteleone's method). Of the first ten, 5 were infections by *P. vivax*, one by *P. falciparum*, and in 4 the infection is not stated; 6 gave a positive result to the injection. Of the second series, 6 were *P. vivax*, 2 *P. malariae* and 2 were not determined, 7 of these gave a positive result. It is concluded that both methods are of value for the purpose.

H. H. S.

KORTEWEG (P. C.). Malaria tertiana als oorzaak van purpura haemorrhagica. [**Malaria as a Cause of Purpura Haemorrhagica.**] —*Nederl. Tijdschr. v. Geneesk.* 1933. Mar. 4. Vol. 77. No. 9. pp. 1011–1014. With 1 chart. English summary (5 lines).

The author gives an account of the development of purpura haemorrhagica in a patient of 20 years of age who had received the usual treatment with malaria blood subcutaneously.

This is a rare complication. The symptoms were vomiting, profuse menstruation, bleeding from the gums and from the nose and petechiae over the trunk and neck. The blood showed definite diminution of blood platelets. As the condition was serious treatment to terminate the malarial infection was necessary. Was this treatment to be quinine

or neosalvarsan? Both are credited with provoking a haemorrhagic diathesis. Quinine, however, was used by intramuscular injection of 0·2 gm. hydrochloride and a cure effected of both the malaria and the purpura. *W. F. Harvey.*

ROBERT (Léopold), PLUCHON & DAREYS. Les albuminuries transitoires des paludéens. [**Transitory Albuminuria in Malaria.**]—*Bull. Soc. Path. Exot.* 1933. Mar. 8. Vol. 26. No. 3. pp. 528–530.

It is important to remember, in countries where yellow fever occurs, that an attack of subtertian malaria is often accompanied by albuminuria. Six cases with *P. falciparum* in the blood and albumen in the urine were admitted to the hospital at Dakar during a period of 59 days. As the temperature came down in a few days with treatment, so the albumen disappeared from the urine. *W. F.*

LALL (Jiwan) & SINGH (Jamiat). **Urobilinuria and its Importance in Malaria.**—*Indian Med. Gaz.* 1933. Mar. Vol. 68. No. 3. pp. 139–141.

Four important conditions in the tropics in which urobilin is present in large amounts are in order of importance: malaria, resolving lobar pneumonia, internal haemorrhage, and cholecystitis. The largest quantity is found in malaria. Details are given of a method of estimating the quantity of urobilin in a colorimeter, by comparison with a standard solution of acriflavine. (See also this *Bulletin*, Vol. 28, pp. 141 and 1025.) *W. F.*

CHOPRA (R. N.), GUPTA (B. M. Das) & SEN (B.). **A Fatal Case of Severe Malignant Tertian Malaria.**—*Indian Med. Gaz.* 1932. Dec. Vol. 67. No. 12. pp. 680–681. With 3 figs. on 1 plate.

More than half the blood cells contained parasites. Three hours after 5 grains of quinine had been given, the number of parasites had increased. Another 8 grains was given, but the patient died five hours later. The blood taken half an hour before death showed a heavy phagocytosis of parasites by the large hyaline and polymorphonuclear cells. *W. F.*

PINELLI (Anna). Un caso di malaria congenita. [**Congenital Malaria.**]—*Pediatria.* 1932. Dec. 15. Vol. 40. No. 24. pp. 1317–1321. [18 refs.]

The history of this patient is very clearly presented. A male infant, on the fifth day after birth when apparently in excellent health, had an attack of fever, temperature 38·4°C. This came down after a few hours, with a sweating, and after 24 hours' apyrexia rose to 39°C., falling similarly with a sweat. The mother had a similar attack at the same time and had suffered from malaria for three years.

Examination of the child showed a spleen extending two fingers'-breadths below the costal margin and the liver one. W.R. negative both in mother and child. The blood of the latter contained red cells 3,950,000, leucocytes 9,500 per cmm., Hb. 70 per cent. Numerous *P. vivax*, sporulating and gametocyte forms, were present. Quinine, 3 doses of 10 cgm., was given and when the next attack was due the fever was less. The drug was then given intramuscularly; after 3 injections the fever disappeared, spleen and liver were reduced and parasites were no longer found in the blood. The mother's blood also contained *P. vivax*.

The presence of parasites and particularly gametocytes in a child 5 days old excludes infection during or after birth and indicates *in utero* infection.

H. H. S.

CHORINE (V.). Un cas de paludisme congénital. [**A Case of Congenital Malaria.**]—*Bull. Soc. Path. Exot.* 1932. Nov. 9. Vol. 25. No. 9. pp. 952–953. With 1 chart.

The author found benign tertian parasites in the blood of a woman both on the day of her confinement and on the day before it. He also found them in the umbilical cord, and in the blood of the child some hours after birth. *W. F.*

HAKKI (Adil) & MUHTAR (Ahmet). Erfahrungen mit Chinoplasmin. [**Experience with Chinoplasmin.**]—*Arch. f. Schiffs- u. Trop.-Hyg.* 1933. Apr. Vol. 37. No. 4. pp. 173–175.

Four cases successfully treated. In two gametocytes were demonstrated by splenic puncture after treatment ; in two not. The authors say that they have confirmed the action of chinoplasmin on the gametocytes, and its superiority to quinine. *A. G. B.*

JARVIS (O. D.). **Further Researches into the Treatment of Chronic Benign Tertian Malaria with Plasmoquine and Quinine.**—*Indian Jl. Med. Res.* 1932. Oct. Vol. 20. No. 2. pp. 627–631.

Major Jarvis, of the Malaria Treatment Centre, Kasauli, recommends a trial of routine treatment with 0·02 gram plasmoquine and 20 grains of quinine daily for a period of 14 days. He states that this treatment can be given to young British soldiers without any fear of toxic symptoms. He found that a 14-day course with 0·03 gram of plasmoquine was as good as a 21-day course with either 0·03 or 0·04 gram (a daily dose of 20 grains of quinine being given in each case). A 21-day course of 0·02 gram plasmoquine with quinine was as efficient in preventing relapse as a 14-day course of 0·03 gram of plasmoquine with quinine. The period of observation averaged 12 weeks.

Treatment.	Daily Dose × Days.		Total cases.	Relapse Rate, per cent.
	Plasmoquine gramme.	Quinine, grains.		
Quinine sulphate*	*Nil*	30 (max.) × 21–56	667	68·0
Plasmoquine†	0·08 × 28	*Nil*	22	22·7
Plasmoquine and Quinine‡	0·04 × 21	20 × 21	44	8·4
"C" (1930)	0·03 × 21	20 × 21	75	8·0
"C" (1931)			31	0·0
"C" Total			106	5·7
"F"	0·02 × 21	20 × 21	10	0·0
"J"	0·03 × 14	20 × 14	10	0·0

*Sinton and Bird, 1929. †Sinton and Bird, 1928. ‡Sinton, Smith and Pottinger, 1930. *W. F.*

GARCIA DE COSA (Cecilia). La asociacion medicamentosa atebrina-plasmoquina, en el tratamiento do las fiebres estio-otoñales. [**Combined Atebrin and Plasmoquine in Subtertian Malaria.**]—*Medicina Países Cálidos.* Madrid. 1933. Jan. Vol. 6. No. 1. pp. 20–26. With 1 fig.

The author notes the frequent occurrence of toxic symptoms when these drugs are given together. When he uses the drugs separately

he gives the plasmoquine with quinine, the course being 21 days for adults, 30 for children. To the former he gives for seven days 0·04 gm. plasmoquine with 1 gm. quinine [? salt], then quinine alone for a week, and the two together again for the third week. With atebrin alone, he gives 0·3 gm. daily in 3 doses for 5 days, 1·5 gm. in all.

When combining the two, he varies his plan, but he obtained the best results and the least subjective disturbance when the drugs were given on alternate days.

The number of patients treated was small, only seventeen. In 5 of them cure resulted after 5 days of plasmoquine; in one of them the gametocytes disappeared in 2 days. Of 9 who had the two drugs together, 8 exhibited gastro-intestinal disturbances and two of them relapsed. In 15 of the 17 the fever came down before the fourth day and did not return. The blood changes are worth noting; with plasmoquine an increase of lymphocytes at the expense of polymorphonuclears is usual, with atebrin there is eosinophilia and some neutrophilia with relative lymphopenia. With the two drugs together the plasmoquine effect predominates, lymphocytosis with neutropenia.

Toxic symptoms were chiefly gastro-intestinal—vomiting, diarrhoea, nausea, headache and in some violent colic—and also plasmoquine cyanosis, and a yellowish discolouration and epistaxis from the atebrin. It is not advisable, therefore, to give the combined treatment to patients with functional or organic gastro-intestinal or circulatory symptoms. *H. H. S.*

HOOPS (A. L.). **The Treatment of Malaria with Atebrin in Estate Practice.**—*Trans. Roy. Soc. Trop. Med. & Hyg.* 1932. Nov. 30. Vol. 26. No. 3. pp. 289–294.

The author finds atebrin cheaper than quinine.

Forty-three patients, comprising 25 subtertian, 15 benign tertian, and 3 quartan infections, were given 0·1 grams of atebrin three times a day for a period of five days. All recovered quickly, except one patient with subtertian who died fifty-four hours after admission, and none relapsed. Plasmoquine 0·03 gram daily was given in addition to subtertian cases. Four patients complained of pains in abdomen, and three showed a temporary, yellow discoloration of the skin. The usual course of quinine treatment on the rubber estates under the author's supervision requires a total of one ounce. This costs two shillings and fourpence, while a five-day course of atebrin costs only two shillings, requires less time, and is not so likely to be followed by relapse. Children stood the treatment well. *W. F.*

MAY (Walter J.). **Atebrin in Malaria.**—*South African Med. Jl.* 1932. Dec. 24. Vol. 6. No. 24. pp. 801–802.

Two daily doses of 0·1 gram of atebrin were given to 32 subtertian cases, 11 benign tertian, and 7 of mixed infection, for a period of 8 days. One patient who was suffering from subtertian died on the fourth day with parasites still present. In two other cases the temperature did not settle down quickly, but in the remainder it came down in one or two days and remained without subsequent rise. In 32 cases which were followed up, there were 5 relapses; and the author thinks that larger doses would probably give better results. *W. F.*

JOLLEY (P. G. E.). **The Results of Atebrin Treatment in Malaria.**—*Malayan Med. Jl.* 1932. Dec. Vol. 7. No. 4. pp. 129–131.

Six cases of benign tertian, two cases of subtertian, one of quartan, and two of mixed benign and subtertian infection, were given 0·1 gram of atebrin three times a day for 5 days. The subtertian cases were given plasmoquine 0·03 gram daily for 5 days in addition. Parasites and symptoms disappeared quickly and none of the patients relapsed during 40 days of subsequent observation. *W. F.*

CHATTERJEE (Sarasi Ranjan). **A Review of Six Cases of Malaria treated with a Erion (Atebrin).**—*Calcutta Med. Jl.* 1932. Sept. Vol. 27. No. 3. pp. 60–63.

Five cases of benign tertian and one of subtertian were treated for 4 or 5 days with 0·3 gram of atebrin daily. Parasites disappeared within two or three days, and in two cases which were under observation for six months there was no relapse. *W. F.*

CHOPRA (R. N.). **Cyanosis after Plasmochin.**—*Indian Med. Gaz.* 1933. Jan. Vol. 68. No. 1. pp. 26–27.

A European, aged 28, was given an average daily dose of 0·05 gram of plasmoquine for 5 days. He suffered from severe pain in the epigastrium, back and neck, and from cyanosis which persisted for 9 days. No methaemoglobin could be detected in the blood. The resistance of the blood cells to haemolytic agents was increased. *W. F.*

LEAGUE OF NATIONS. HEALTH ORGANISATION. **Enquiry into the Quinine Requirements of Malarial Countries and the World Prevalence of Malaria.** L.o.N.P. III. Health. 1932. III. 3.—89 pp. Geneva. [Allen & Unwin, Ltd., 40 Museum Street, London, W.C.1.] [3s.; $0·75].

The Committee estimates the quinine requirements of the world at 1,387,411 kilograms per annum.

The Health Organization asked the health departments of malarial countries, by means of a circular letter dated January 14th 1931, for certain particulars relating to malaria, especially as regards the prevalence of the disease, the amount of quinine imported annually, and the amount which would be required to meet all the needs of the country. The data, which have been supplied by 93 countries, form a unique collection of material; they have been studied by a Reporting Committee consisting of Professor NOCHT, Professor PITTALUGA, and Dr. A. T. STANTON, and also by the Alkaloids Sub-Committee of the Malaria Commission. The Health Committee is of opinion that they may form the basis of a future conference on quinine.

The total number of cases treated in the countries concerned, during the last year of the enquiry, was 17,750,760; an increase of more than a million over the average for recent years, which is attributed to the development of health services and anti-malaria organizations. Though the number of cases receiving treatment has increased, it still falls short, by many millions, of the number standing in need of it. In India, out of 100 million malaria cases, only 8 to 10 millions are treated, and the quantity of quinine distributed does not exceed 2 grams per annum per case treated; there are many other countries where the conditions of treatment are similar. The Committee concludes that the

world consumption of quinine is still far below the minimum necessary, and, estimating on the basis of a standard dose of 20 grams per case per annum, they arrive at the figure of 1,387,411 kilograms as representing the total amount required annually. *W. F.*

LANCET. 1933. Mar. 11. pp. 537–538.—**The Production of Quinine.**

Messrs. Howards & Sons state that the quinine industry could supply all the quinine which the League of Nations estimate as necessary for the whole world.

The Health Organization of the League of Nations, having estimated that 1,387,000 kilograms of quinine per annum is required for the treatment of all malaria patients in the world (see above), the question has been raised whether such a demand could be met by the quinine industry. Messrs. Howards & Sons affirm that it could. The normal sales of the 14 principal factories are about 500,000 kilograms yearly. With their existing plant they could double this output. Large stocks of quinine are kept in stock, and while these were being drawn upon, extra plant could be erected. Huge stocks of bark are also held, and the cinchona plantations are at present collecting only about half of their possible harvest. The difficulty is wholly economic. No world shortage of the drug exists, but the peoples and governments of malarious countries cannot afford to buy it in adequate amounts.

W. F.

LEGER (Marcel). Le paludisme, comme la syphilis, est justiciable d'un traitement continu et non de cures intermittentes "d'entretien." [**The Treatment of Malaria should be Continuous.**]—*Arch. Inst. Prophylactique.* 1933. Vol. 5. No. 1. pp. 76–101. [36 refs.] English summary.

The author's thesis is that relapses are the result of faulty treatment, and can be avoided by his method of continuous treatment over several months.

He considers that each of the three species of plasmodium has its own site of election in the body: for *P. vivax*, this is the spleen; for *P. falciparum* it is the central nervous system; for *P. malariae* it may be the bone-marrow or the kidneys. When, late in the disease, these strongholds are occupied, longer treatment is necessary than in primary attacks. The treatment recommended for subtertian malaria consists of alternate courses of quinine and plasmoquine, continued for 3 months if it is a primary attack, or for 5 months if it is not. A similar treatment is prescribed for quartan malaria, but the duration is longer; namely 5 months for a primary, and 7 months for a later attack. The duration of treatment for benign tertian is the same, but, in this form of malaria, stovarsol is employed in addition to plasmoquine and quinine. [The stumbling block would be the patient; even though the author does not favour the brutal method of giving quinine in solution.]

W. F.

MASSIAS (C.). Le 710 et le quiniostovarsol dans le traitement du paludisme à *Plasmodium vivax* et à *Plasmodium praecox.* [**Quiniostovarsol and 710 in Malarial Treatment.**]—*Bull. Soc. Path. Exot.* 1933. Mar. 8. Vol. 26. No. 3. pp. 433–438. With 4 charts.

The daily quantities recommended are 1·0 gram of quiniostovarsol and 0·08 gram of 710, divided into two or more doses and given before

meals. A course lasts 7 to 10 days, and there should be an interval of at least 7 days before it is repeated. The drugs must be stored carefully, especially in hot countries, and they are best dispensed in compressed tablets. The treatment was given to 6 benign tertian and 4 sub-tertian patients, with the result that the parasites quickly disappeared. The Annamite patients refused to stay in hospital more than a few days, and the action of the drugs on crescents was not very clear. There was no vomiting.

[There are several dangerous misprints in this article : a daily dose of 0·88 gram of 710 is recommended in one place, when obviously 0·08 is intended ; in another place, it is stated that a patient took 8·20 grams of 710 in 3 days. In both instances the figure 8 appears to have been printed in place of 0.] *W. F.*

SAUTET (J.). Traitement du paludisme par le 710 et le 574 associés ou non à la quinine ou au quiniostovarsol. [**Treatment of Malaria with 710 and 574 Alone and in Association with Quinine or Quiniostovarsol.**]—*Bull. Soc. Path. Exot.* 1932. Dec. 14. Vol. 25. No. 10. pp. 1074–1091. With 6 charts.

The author concludes that Fourneau 710 in association with quiniostovarsol is the best treatment for all three forms of malaria, and brings about rapid disappearance of crescents. His results with Fourneau 574 were not so good.

He recommends the following doses :—One cachet containing 0·02 gram of 710, and 0·25 gram of quiniostovarsol, four times a day ; two courses, each of 7 days duration, with an interval of 5 days between. One batch of cachets was highly toxic, but the others produced no side effects except giddiness in susceptible persons. Fourneau 710 in association with quinine also gave good results, but when it was given alone, it failed to destroy the parasites. Fourneau 710 is diethylamino propylaminomethoxy quinoline, and 574 is the corresponding dimethyl derivative. [Clinical notes of the treated cases are given, but they are rather difficult to follow, and it is not easy to see how the author reached the conclusion that crescents are quickly destroyed by 710 and quiniostovarsol.] *W. F.*

BEVIL (H. G.). **Hydroquinidine in Malaria.**—*Amer. Jl. Trop. Med.* 1932. Nov. Vol. 12. No. 6. pp. 473–476.

Hydroquinidine was given to 16 cases of malaria with immediate results at least equal to quinine and without toxic side effects. In one case 10 grains were given daily for 48 days, followed by 5 grains daily for a further period of 25 days. Hydroquinidine is a dextro-rotatory alkaloid derived from cinchona bark ; it differs from quinidine only in containing two more atoms of hydrogen. It is an almost constant impurity of quinidine. *W. F.*

ROBERTS (A. M.) & LEACH (C. W.). **Quartan Malaria. Report of Case. Treatment with Quinidin Sulphate in a Patient Hypersensitive to Quinin.**—*California & Western Med.* 1932. Nov. Vol. 37. No. 5. pp. 315–317. With 1 fig. [25 refs.]

Records a case of quartan malaria in California, in a patient hypersensitive to quinine, and his successful treatment with quinidine (this *Bulletin*, Vol. 29, p. 352).

A dose of a quarter of a grain of quinine sulphate, by the mouth, was followed 20 minutes later by vomiting, itching, erythema, urticaria and lachrymation. The symptoms were relieved by an injection of adrenalin.

W. F.

KIKUTH (W.). Chemotherapeutische Versuche mit neuen synthetischen Malariamitteln in ihrer Bedeutung für die Bekämpfung der Malaria. [**Chemotherapeutic Experiments with New Synthetic Malarial Remedies.**]—*Zent. f. Bakt.* I. Abt. Orig. 1932. Vol. 127. No. 1/3. Beiheft pp. 172*–178.* With 2 figs. on 1 plate.

The author found that when he employed a haemoproteus infection in the finch for testing his synthetic malarial remedies he got much more satisfactory results than when he used the *Plasmodium praecox* infection of canaries for the purpose.

The advantage of the haemoproteus infection is that in many respects it is analogous to the *Plasmodium falciparum* infection of man. The gametocytes are found in the peripheral blood and have a certain resemblance to the crescents of *P. falciparum*. The asexual forms are not found in the peripheral blood, but inhabit the endothelial cells of the internal organs. By using this infection as a test he was able to bring out quite clearly the now well known differences in action of quinine, atebrin and plasmoquine. His experimental findings have been fully confirmed by extensive clinical trials of the drugs. He considers that atebrin has very definite therapeutic advantages over quinine.

E. D. W. Greig.

BAKER (J. N.) & GILL (D. G.). **Plasmochin in Malaria Prevention. Experiments in Alabama.**—*Public Health Rep.* 1932. Dec. 2. Vol. 47. No. 49. pp. 2245–2250. With 1 chart.

The authors conclude that plasmoquine compound in a dose of one or two tablets a week, administered to all the inhabitants of a district, will materially lessen the incidence of malaria. Each tablet contains 0·01 gram of plasmoquine and 0·125 gram of quinine.

Two rural areas were chosen in Alabama, and from June to October every person was given one tablet every week. In 1929 the attack ratios per 100 had been 73 and 62 ; in 1930 they were 18 and 6. In two control areas the figures were 73 and 35 in 1929, and 31 and 7 in 1930. In 1931, another area was chosen and one tablet was given twice a week from June to November. The attack rate in this area was 20 in 1930, and 3·5 in 1931. In the control area it was 12 in 1930, and 9 in 1931.

W. F.

RICE (Justus B.). **Experiments on Plasmoquine as a Prophylactic among West African Negroes exposed to Bites of *A. costalis* infected with Subtertian Malaria.**—*Ann. Trop. Med. & Parasit.* 1932. Dec. 16. Vol. 26. No. 4. pp. 555–576. [10 refs.]

The author finds that 0·03 gram of plasmoquine a day can be taken for several months without any untoward symptoms, and that a daily dose of 0·023 gram will protect a man weighing 10 stone 10 lbs. against subtertian malaria.

These experiments were carried out on 42 Africans and one European in Liberia. The volunteers were first given a course of plasmoquine and quinine in order to insure that the blood was free from naturally

acquired infection. Plasmoquine was then continued in various doses, and, after the volunteers had been taking it for a month or more, they were bitten by *Anopheles costalis*, which had been infected in the laboratory with *P. falciparum*; the plasmoquine was then continued for at least another month. It was found that daily doses above 0·34 milligram per kilo of body weight were sufficient to protect. The plasmoquine was given as a single dose each day, after the noon meal, and appeared to be effective over the 24 hours. Most Europeans in Liberia contract malaria during the first three or four months of residence, in spite of quinine prophylaxis; but two who have taken regular daily doses of plasmoquine, since their arrival 14 months ago, have remained free.

One reason why the author's results were so much better than SWELLENGREBEL's (this *Bulletin*, Vol. 29, p. 37) may be that plasmoquine is a better protector against subtertian malaria than against the benign tertian strain employed by SWELLENGREBEL. It must also be remembered that these experiments were carried out on members of an African population saturated with malaria from childhood, and it is possible that larger doses are required to protect those who have never been infected before. *W. F.*

STRICKLAND (C.) & ROY (D. N.). **The Prophylaxis of Malaria by Drugs.** —*Parasitology*. 1933. Feb. Vol. 25. No. 1. pp. 77–86.

The authors conclude "that there is no prophylactic drug action against sporozoites demonstrated for malaria, and the effects hitherto observed must be considered to be a therapeutic action of the drugs on the parasites developing in man."

Quinoplasmine given to seven volunteers before they were bitten by infected *A. stephensi*, did not prevent malaria, though in one case where 0·1 gram of plasmoquine and 45 grains of quinine were given within 31 hours of the biting the incubation was delayed to the nineteenth day, and the attack was modified. Quinoplasmine given before and soon after the biting also failed to prevent infection. Similar experiments were made with quinine. Fifty-four grains given within the 48 hours before the biting did not prevent infection, nor did 5 grains daily for 14 days after the biting. *W. F.*

SOESILO (R.), GILBERT (A. P. W.) & BAGINDO (Zahar Gelar Soetan). Een en ander over malariaprophylaxe en Atebrin (eerste mededeeling). [**Notes on Malaria Prophylaxis and Atebrin.**]—*Geneesk. Tijdschr. v. Nederl.-Indië.* 1933. Jan. 31. Vol. 73. No. 3. pp. 153–170. With 9 figs. [28 refs.]

The field traversed in this article is not restricted to the use of atebrin, but the most important part is the work done by the authors with atebrin prophylactically and therapeutically.

Volunteers were infected by the bite of certainly infective mosquitoes (*A. subpictus*), which had received their infection from patients showing not less than 5 gametes per 1,000 leucocytes. The results as summarized, were:—(1) Six out of 21 volunteers treated prophylactically with atebrin and bitten by infected mosquitoes showed parasites in their blood after 12 to 24 days and rise of temperature after 15 to 24 days. (2) Ten out of 11 volunteers receiving no atebrin (controls) showed parasites in their blood after 8 to 13 days and rise of temperature after 10 to 14 days. (3) Seventeen infected volunteers were treated with 100 mgm. atebrin thrice daily for 5 to 6 days. In 4 of these the

treatment was begun before and in 13 after the appearance of fever. Frequent examinations for 2 to 4 months in 13, and for one month in 3 of these, after the stoppage of the treatment, showed neither schizonts nor gametes. One person only of the 17 treated developed fever with parasites about two months after the last dose of atebrin. No objectionable symptoms were met with. (4) Atebrin acts quickly upon tropica rings and mature schizonts and appears to prevent gamete formation. (5) Two patients, having naturally contracted tertian malaria, were successfully treated with atebrin. *W. F. Harvey.*

STAUDT (H.). Sur la quininisation préventive au Katanga. [**Prophylactic Quinine at Katanga.**]—*Bull. Méd. du Katanga.* 1932. Vol. 9. No. 5. pp. 121, 123–8, 131.

Quininization of native children promotes their well-being, and reduces sickness and mortality, but it does not cure them or prevent re-infection, and cannot solve the problem of malaria. The best results are obtained by the administration of 8 grains a day for 15 days, followed by a continuous preventive treatment of about 4 grains a day. This is for children between 5 and 15 years old. *W. F.*

GORDON (R. M.) & DAVEY (T. H.). **A Note on the Value of issuing Free Quinine to Native Infants.** [Miscellanea.]—*Ann. Trop. Med. & Parasit.* 1933. Apr. 10. Vol. 27. No. 1. p. 179.

It has been the custom to supply euquinine for all infants brought to the clinic, Freetown. The results of examining the blood of such infants, and of controls who had received no quinine, have shown that the percentage of children infected with malaria is practically the same in the two groups. This method of supplying quinine to be taken home and administered by the mother is obviously unsatisfactory. Probably it is not given to the infants. *W. F.*

CORRADETTI (Augusto). Le reazioni di Henry nell' infezione malarica. (**Henry's Reactions in Malaria.**)—*Riv. di Malariologia.* 1932. May–June. Vol. 11. No. 3. pp 282–300. [71 refs.] English summary p. 413.

The author records his personal experiences with these tests in a considerable number of patients infected with different forms of malaria plasmodium. In all cases he employed both the Ferro- and the Melano-flocculation. His findings may be summarized as follows :—

Of 55 patients actually suffering from malaria—19 with benign tertian, 32 subtertian, two with both these, one with quartan and one with benign tertian—the only ones giving a negative with both tests were 3 subtertian and one benign tertian infections ; 5 gave a negative ferro-flocculation with positive melano-flocculation, 3 subtertian, one natural benign tertian and a general paralytic in his sixteenth attack after inoculated *P. vivax.* None gave a positive ferro- with a negative melano-flocculation.

Of 25 chronic malaria patients 19 gave a double positive, 3 a double negative, and 2 a negative ferro- with positive melano-flocculation.

Of 13 patients suffering from various affections unconnected with malaria but giving a history of malaria long previously, one only gave a double positive, all the rest was negative to both.

Of 63 from whom no history of past or recent malaria was obtainable, three gave a double positive, two cases of leucaemia and one of pernicious anaemia ; two others with a history of infection 7 and 13 years ago gave a negative.

The author concludes that :—

1. The reactions are specific of malarial infection [there were three exceptions in the blood conditions mentioned above].
2. If the blood is taken during the fever or during digestion the reaction may be weak or negative.
3. Treatment by quinine may make it negative, even during an attack, but in chronic malaria, it remains positive in spite of quinine.
4. If there is a strong suspicion, on clinical grounds, that the condition is malarial, the test if negative should be repeated. *H. H. S.*

TRENSZ (F.). Recherches sur la " séro-floculation palustre" (réaction de Henry). [**Henry's Reaction.**]—*Arch. Inst. Pasteur d'Algérie.* 1932. Dec. Vol. 10. No. 4. pp. 443–463. With 3 figs.

Henry's reaction is not specific ; it is positive in trypanosomiasis and leishmaniasis. The flocculation is not a reaction between melanin and its antibody.

It is uncertain whether repeatedly negative Henry tests mean that a patient is definitely cured. HENRY himself states that where the infection is latent and inactive the test may be negative. The author tested 12 healthy men who had suffered from malaria in the past, but had had no manifestations for several years. Eleven were negative ; the twelfth, who had not had an attack for six years, gave a faintly positive reaction and, several weeks later, he had an attack of benign tertian. HENRY considers that the melanin and the ochre pigment produced in malaria act as antigens (" endogens ") and produce specific antibodies which flocculate with his artificial melanin and iron solutions. The author denies that the reaction is due to these antibodies, or that it is specific. He has found it positive not only in malaria, but also in other protozoal diseases in which no melanin is produced, namely trypanosomiasis and leishmaniasis (Vol. 29, p. 715). He attributes it to an instability of the serum which occurs in protozoal diseases. In 11 guineapigs inoculated with trypanosomes (*T. berberum*) the reaction became positive soon after the appearance of trypanosomes, and as the reaction became stronger, " surflocculance " occurred in 6 of the control tubes containing only distilled water and serum. The difference between the flocculation in the tubes of test, and the " surflocculance " in the control tubes, is only a matter of degree —Henry's reagents assist the flocculation. Henry's reaction is useless as a measure of the amount of malaria in a district. The author examined the inhabitants of a native village and found that while the spleen and parasite rates rose in the malaria season, the positive Henry tests decreased ; again, while the spleen and parasite rates decreased with age, the positive Henry tests increased. *W. F.*

TZECHNOWITZER (M. M.), GORCHOWA (E. L.) & MOLDAVSKAJA-KRITSCHEWSKAJA (W. D.). Die Melanoflockulation bei Malaria. [**Melanoflocculation Reaction in Malaria.**]—*Zent. f. Bakt.* I. Abt. Orig. 1932. Dec. 15. Vol. 126. No. 5/6. pp. 419–427. With 2 figs. [11 refs.]

In the reaction of melanoflocculation, RMF, the authors employed the choroid of rabbits' eyes in place of the choroid from the eye of the

ox, and found it equally efficient as a source of antigen. Also they determined experimentally the most suitable dilution of saline for use with the antigen and found that 1–750 gave the best results. They worked out a simplified scheme for the reaction, which is shown in the following table :—

No. of test tube.	Antigen in NaCl 1–750	Serum	NaCl 1–750
1	0·25	2 drops	—
2	0·25	—	2 drops
3	—	2 drops	0·25

The RMF was tested in 1,220 sera, but critically analysed in 998 cases only. 736 of the cases were malarial infections and the remainder were cases of other diseases. Of the 736 cases of malaria, 432 patients attended the hospital of the Institute in the Ukraine, 290 were examined during the expedition to Melitopol, 14 were cases of malariatherapy. Of the 432 cases, 93 were primary infections, 153 were relapse cases, in the remainder the diagnosis was from history only. Of the primary infections 92 were tested and the RMF was positive in 89 (96·7 per cent.) ; in 48 of the cases of primary infection the parasites found in the blood were, 45 *P. vivax*, 1 *P. falciparum*, 1 mixed ; the RMF was positive in all these cases. In 153 cases of relapsing malaria the RMF was positive in 136 (86·2 per cent.), negative in 17 (13·8 per cent.) ; parasites were found in the blood of 66 relapse cases and in all, except one case, the RMF was positive. In 187 cases, in which the diagnosis was based only on the history, the reaction was positive in 17 (9 per cent.), doubtful in 30 (16·2 per cent.), negative in 140 (74·8 per cent.). During the Melitopol expedition there was an agreement between the positive RMF and the finding of parasites in the blood in 94·4 per cent. of the cases. The conclusion is drawn by the authors from their observations that there is almost complete correlation between the presence of parasites in the blood and the occurrence of a positive RMF, which varies from 94·2 to 99 per cent. ; therefore the RMF must be looked upon as pathognomonic for malaria. Of control sera 47, sent for Wassermann test, were investigated and 17 (42 per cent.) gave a positive RMF, but of 341 malarial sera tested for W.R., 11·1 per cent. were positive ; further, in syphilitics it is not possible to exclude a concomitant malarial infection.

The RMF was found negative in a large series of cases, viz., syphilis, tuberculosis, carcinoma, typhoid, erysipelas, dermal leishmaniasis, as well as in series of septic infections ; in typhus it is distinctly positive.

This serological index, which the authors consider of great importance from the epidemiological point of view, was applied to two villages of the Melitopol district, one heavily and one moderately infected with malaria. The following table shows the results.

Indices of amount of malaria.	Parasites in 135 persons.	Spleen in 218 persons.	History in 203 persons.	Serological in 290 persons.
Heavy ...	53·2	59·5	92·7	83·5
Moderate ...	7·1	7·1	64·2	57·1

The authors point out that the table shows clearly that the serological index and history are in close correspondence.

E. D. W. Greig.

CHORINE (V.). Réaction de Henry dans le diagnostic du paludisme. (**Henry's Reaction in the Diagnosis of Malaria.**)—*Riv. di Malariologia.* 1932. May–June. Vol. 11. No. 3. pp. 273–281. [30 refs.] English summary (7 lines) p. 413.

The author concludes that a repeatedly negative reaction signifies the absence of malaria infection, a positive reaction indicates its probability, but does not permit its definite diagnosis. A table is given showing the lay-out of the tubes for the test.

An excellent and concise review of the subject is given. The reaction is negative during the malaria paroxysm because the antibodies are fixed by the melanin and iron pigment derived from the rupture of the schizonts. It is positive in diseases other than malaria, in which intense and rapid blood destruction occurs. TRENSZ (above) has found it positive in guineapigs with trypanosomiasis, and in dogs with leishmaniasis. The author examined: (1) Old war cases of malaria 49: negative 46; positive 3, melanoreaction strongly positive, ferroreaction feeble or negative. No parasites. (2) Persons more or less recently returned from the Colonies 67: 63 negative; 4 positive, and parasites found in two of these. (3) General paralytics inoculated with benign tertian and treated with quinine 21: 8 negative, all free from parasites; 13 positive, 5 with parasites. *W. F.*

CHORINE (V.). Evolution de la réaction de Henry et surfloculance du sérum. [**The Development of Henry's Reaction. Surflocculance.**]—*Bull. Soc. Path. Exot.* 1933. Feb. 8 & 9. Vol. 26. No. 2. pp. 269–273. With 1 fig.

Henry's reaction appears soon after the inoculation of malaria, rises to a maximum, and disappears during quinine treatment.

The reaction was studied in general paralytics inoculated with *P. vivax.* The first paroxysm usually occurred 2 to 10 days after the inoculation. Henry's melanoreaction became positive on the 3rd or 4th day, irrespective of whether a paroxysm had occurred or not. The ferroreaction appeared later. The intensity of the reaction increased until the 6th or 7th paroxysm. When quinine was given, the reaction remained stationary for 12 days; it then declined and disappeared in about 35 days. The reaction became negative during each paroxysm, and appeared again 4 hours later. When the serum was heated for half an hour at 60°C. it no longer reacted. The author does not agree with TRENSZ (above) that the flocculation of malarial sera in distilled water (*surflocculance*), and Henry's melanoreaction are manifestations of the same phenomenon, differing only in degree. *W. F.*

HENRY (A. F. X.). Mélanofloculation. Formolage des tubes témoins; alcalinisation des liquides de dilution. [**Formalin and Alkalization in Melanoflocculation.**]—*C. R. Soc. Biol.* 1933. Mar. 3. Vol. 112. No. 8. pp. 765–768.

The stock solution of melanin for Henry's reaction is preserved by the addition of 0·5 per cent. formol. This solution is diluted 1 in 10 during the test, so that the final strength of formol is only 1 in 2,000.

The author used to add formol in corresponding quantity to the control tubes, but he abandoned the practice because it introduced complications and was generally unnecessary. He now points out that kala azar sera are gelidified in the tubes containing melanine, because of the formol in it. In places where there is kala azar it is therefore necessary to have formol in the control tubes in order to avoid the reading of false reactions. To avoid the production of acidity, 0·25 cc. of N/100 caustic soda should be added to each 100 cc. of the distilled water and of the saline water used in the reaction. *W. F.*

MEERSSEMAN (F.) & LACOUR (P.). Recherches sur la réaction de la malaria-floculation de Henry. [**Henry's Reaction.**]—*C. R. Soc. Biol.* 1933. Mar. 10. Vol. 112. No. 9. pp. 908–910.

The authors bring forward evidence to show that the reaction is specific and does not give positive results in other diseases, not even in trypanosomiasis.

They insist on careful technique. The test should be made simultaneously in distilled water and in saline, 1 in 1,000 for the ferro-flocculation, and 1 in 3,000 for the melanoflocculation. The reaction is more sensitive in the distilled water ; the salt solution is of value in cases where the serum flocculates spontaneously with water. The reaction tubes should be formolized to the same titre as the antigen, in the melanoreaction. Their results were as follows : (1) 22 cases of malaria with parasites in the blood gave 22 positives. (2) 23 cases with enlarged spleens, but free from parasites and without attacks for at least 6 months, gave 22 positives. (3) 37 cases who had suffered from malaria during the war, but had not done so later, gave only 2 positives. The controls were as follows : (*a*) 13 healthy persons gave no positives ; (*b*) 40 persons with respiratory diseases gave one doubtful positive ; (*c*) 11 syphilitics gave 1 positive ; (*d*) 4 cases of hypertrophic cirrhosis and 2 cases of gastric cancer, gave no positives ; (*e*) two cases of sleeping sickness and a guineapig infected with trypanosomiasis, gave no positive reactions. (See TRENSZ above, and 1932, Vol. 29, p. 715.) *W. F.*

FARJOT. Résultats de cent séro-floculations de Henry. [**Henry's Serofloccculation.**]—*Bull. Soc. Path. Exot.* 1933. Mar. 8. Vol. 26. No. 3. pp. 428–432.

In cases of syphilis with a strongly positive Wassermann reaction, the reaction of Henry may also be positive, apart from malarial infection.

Four malaria patients with parasites in the blood were examined 11 times. They were all positive. One became negative after treatment with quinine. Twenty-one persons without parasites, but who had had malaria within six years, gave 13 positives and 8 negatives. Seven persons who had had malaria more than six years before gave 1 positive and 6 negatives. Thirty-three persons who had never had malaria were examined as controls ; of these, 29 were negative and 4 were positive. Three of the 4 positives were syphilitics, the other was suffering from tuberculosis and gave a strong flocculation with resorcin. These results led the author to apply Henry's test to a small group of syphilitics. Four with a very feeble Wassermann reaction gave negative Henry tests, and 3 with a strongly positive Wassermann reaction gave a positive Henry's reaction, though they had never had malaria. *W. F.*

ASCIONE (Guglielmo) & MARIOTTI (Ettore). Sul passaggio dei parassiti malarici nel liquido cerebro-spinale e loro comportamento verso le candele porose. (**On the Passage of Malarial Parasites in the Cerebro-Spinal Fluid, and their Behaviour towards the Diatomaceous Earth Filters.**)—*Riv. di Malariologia.* 1932. July–Aug. Vol. 11. No. 4. pp. 417–425. With 14 charts on 5 plates. English summary p. 549.

"The cerebro-spinal fluid (5 experiments) and blood (5 experiments) taken from tertian patients during the fever attacks, were passed through the Berkefeld V and N filters. The intravenous or intrarrhachidian inoculation of the filtrate in psychopathic patients, reproduced the fever attacks after a period of incubation which generally lasted from 10 to 12 days. The accesses were mild, and sometimes irregular, and some relapses were observed. During the first fever accesses malarial parasites were not found in the peripheral blood and in the spleens of these patients, but they appeared during the successive attacks, except in 4 cases. The blood of two of these cases was capable of producing fever symptoms in other mental patients, in whom parasites were also observed."

A number of temperature charts are reproduced. *A. G. B.*

MARCHOUX (E.), LEROY (R.) & CHORINE (V.). Essais infructueux de filtration du paludisme. [**Unsuccessful Attempts to filter Malaria Parasites.**]—*Bull. Soc. Path. Exot.* 1933. Feb. 8 & 9. Vol. 26. No. 2. pp. 260–266.

The infectivity of cerebrospinal fluid is due to the presence of infected red cells, and is removed by filtration.

ASCIONE and MARIOTTI reported that the cerebrospinal fluid, in malaria, contained invisible parasites which would pass through Berkefeld V and N. candles, and would convey infection when the filtrate was inoculated into susceptible subjects. They also reported that citrated plasma was infective after filtration. The authors found that the cerebrospinal fluid was infective during an attack of malaria. After centrifuging at high speed, malaria parasites were demonstrated at the bottom of the tube, and the supernatant fluid was no longer infective. Filtration through a Berkefeld N. candle removed the parasites and the fluid was no longer infective. Samples of cerebrospinal fluid always contain a few red cells originating from vessels wounded during the introduction of the canula, and the malaria parasites gain access to the fluid in this way. The red cells break up and disappear with centrifugation at high speed and cannot be demonstrated unless they are fixed beforehand by the addition of a few drops of osmic acid. This may be the explanation of the statement made by ASCIONE and MARIOTTI. *W. F.*

TAREEV (E. M.) & GONTAEWA (A. A.). Zur Bestimmung des Albumin-Globulin-Mischungsverhältnisses im Blutserum bei Malaria. [**Albumin-Globulin Ratio of the Blood Serum in Malaria.**]—*Arch. f. Schiffs- u. Trop.-Hyg.* 1933. Jan. Vol. 37. No. 1. pp. 28–37. With 1 fig. [16 refs.]

The authors refer to the important research work of LLOYD & PAUL in Calcutta [see this *Bulletin*, Vol. 27, p. 561]. For the determination of the ratio the simpler method of Rusznyak was used. They examined 58 cases, 43 of natural malaria and 15 with inoculated malaria; the

latter were cases of general paralysis and were the most interesting. In general paralysis there is an increase of the globulin fraction. They conclude that :—The albumin-globulin coefficient of the serum is lowered in most cases of malaria. In experimental malaria the albumin-globulin ratio falls with number of rigors and with the termination of the fever it returns to normal. The coefficient and the sedimentation rate of red cells vary inversely. The reduction in the serum albumin coefficient has no value for differential diagnosis of malaria as it occurs in other infections and intoxications.

E. D. W. Greig.

BENHAMOU (E.). Les réticulocytes dans le paludisme. [**Reticulocytes in Malaria.**]—*Bull. Soc. Path. Exot.* 1933. Mar. 8. Vol. 28. No. 3. pp. 426–427.

The normal percentage of reticulocytes, as demonstrated by vital staining, is between 0·5 and 1·5. The number is increased in malaria in consequence of the response of the bone marrow to the destruction of blood corpuscles, and percentages of 3, 4 and 5 are frequently seen with red blood counts between 3,500,000 and 4,500,000. In one severe case with a count of only 1,300,000 red cells, there were 19 per cent. of reticulocytes. *W. F.*

MATHESON (Robert), BOYD (Mark F.) & STRATMAN-THOMAS (Warren K.). *Anopheles Walkeri*, **Theobald, as a Vector of** *Plasmodium vivax*, **Grassi and Feletti.**—*Amer. Jl. Hyg.* 1933. Mar. Vol. 17. No. 2. pp. 515–516.

Specimens of this mosquito caught at Ithaca, New York, were sent by air mail to the Station for Malaria Research at Tallahassee, Florida, where they were fed on a case of benign tertian malaria. They were then kept at a cool temperature, between 19° and 22·8°C. Four out of six became infected and the disease was conveyed to a patient by their bites. The incubation period in these mosquitoes is about 17 days. *W. F.*

CHORINE (V.). Essais de culture de *Plasmodium falciparum*. Action de l'acide carbonique. [**Carbonic Acid in Cultures of** *P. falciparum*.]—*Bull. Soc. Path. Exot.* 1932. Nov. 9. Vol. 25. No. 9. pp. 953–955.

A reaction of pH 7·3 is the most suitable for blood cultures. This can be adjusted by passing carbon dioxide through the medium, or by adding hydrochloric acid. *P. falciparum* can be kept alive for five generations by subculturing every one or two days into defibrinated blood containing glucose and adjusted to this reaction. *W. F.*

BOUCHER (H.). Etude du sang des paludéens (à *Plasmodium vivax*) par les colorations vitales au rouge neutre et au bleu crésyl brillant. [**Vital Staining in Malaria.**]—*C. R. Soc. Biol.* 1933. Feb. 10. Vol. 112. No. 5. pp. 468–471. With 16 figs.

A saturated solution of neutral red, or of Grübler's brilliant cresyl blue, is made in absolute alcohol. This is then brought down to half saturation by adding an equal quantity of alcohol. A few drops of stain are poured

on to a slide which is tilted in order to distribute it evenly over the surface, where it dries as a thin pellicle. The drop of blood for examination is taken on to this stained slide, covered with a cover-slip, luted round the edges with paraffin and put in the incubator for 5 to 10 minutes. The cresyl blue stains the parasites well. *P. vivax* contains granules stained by neutral red when the parasite is alive. *W. F.*

GREEN (Richard). **A Rapid Method of Staining and Mounting Mid-Guts of Mosquitoes for the Demonstration of Oocysts.**—*Parasitology.* 1932. Oct. Vol. 24. No. 3. pp. 305–306.

The midgut is fixed by running 1 per cent. formaldehyde in normal saline under the coverslip. It is stained with Pugh's toluidine blue; dehydrated with acetone; and mounted in Canada balsam or euparal.

W. F.

MORISHITA (Kaoru). **The Useful Points of Alkali-staining for the Examination of Malaria Parasites.**—*Taiwan Igakkai Zasshi* (*Jl. Med. Assoc. Formosa*). 1932. Nov. Vol. 31. No. 11 (332). [In Japanese. With 1 plate. English summary pp. 110–111.]

The author recommends the use of alkaline distilled water (alkali-dilution 0·003 per cent.) to which Merck's Giemsa is added in the proportion of 1 drop to 1 cc. The duration of staining should be 1 hour. *W. F.*

BOYD (Mark F.) & STRATMAN-THOMAS (Warren K.). **A Controlled Technique for the Employment of Naturally Induced Malaria in the Therapy of Paresis.**—*Amer. Jl. Hyg.* 1933. Jan. Vol. 17. No. 1. pp. 37–54.

The simple method of inducing malaria by the inoculation of blood from a malaria patient has been criticized because of the possibility of transferring neurotropic strains of the syphilitic virus, or other infections, from which the donor may be suffering. In view of this possibility, the British Ministry of Health has prohibited the use of malaria therapy under these conditions. The authors here present an account of the technique employed by them in Florida in maintaining strains of *P. vivax* in mosquitoes for therapeutic purposes. They have found some strains much less virulent than others. They do not accept statements to the effect that in some institutions there are strains of *P. vivax* which, after repeated passage by blood inoculation, have lost their power to produce gametocytes (*ante*, p. 87). Such assertions are probably made by those who are "but slightly familiar with the morphology of the parasites." *W. F.*

SMITH (A. W. H.). **Therapeutic Malarialization of General Paralytics in the Tropics.**—*Jl. Mental Sci.* 1933. Jan. Vol. 79. No. 324. pp. 94–101. [17 refs.]

Malaria exists throughout the whole of the Malay Peninsula, but, in spite of this, general paralysis of the insane is as common as in Europe. Therapeutic malaria is comparatively useless. At the Central Mental Hospital (2,500 inmates) 56 patients were inoculated with the result that only 3 were discharged. Forty-two failed to contract malaria, although they were re-inoculated several times, and may be presumed to have some degree of immunity. *W. F.*

CIUCA (M.), BALLIF (L.) & VIERU (M. Chelarescu). Contribution à l'étude de l'infection paludéenne, intentionnellement provoquée par inoculation de sang virulent de tierce bénigne, de fièvre quarte et de Laverania. [**Inoculation Malaria with the Three Species of Malaria Parasites.**]—*Bull. Soc. Path. Exot.* 1933. Feb. 8 & 9. Vol. 26. No. 2. pp. 300–305.

A large proportion of the population of Rumania is immune, especially to *P. vivax*. Strains of *P. malariae* and *P. falciparum* are therefore employed, in addition, for therapeutic inoculation. About 30 per cent. are immune to *P. vivax* and 20 per cent. to *P. falciparum*. The authors found, by the inoculation of susceptible persons with the blood of immune patients, that the immunity was often due to a latent infection—a *premunition*, such as SERGENT has described in the malaria of birds. *W. F.*

LEISERMANN (L. I.). Die experimentelle Malaria beim Menschen. [**Human Experimental Malaria.**]—*Arch. f. Schiffs- u. Trop.-Hyg.* 1932. Dec. Vol. 36. No. 12. pp. 650–671. With 15 figs. [43 refs.]

The author's observations commenced in 1924 and his material was obtained from 253 patients (226 men and 27 women) treated with malaria for various diseases. His strains were obtained from 14 cases of spontaneous malaria (13 cases *P. vivax* and 1 *P. vivax* and *P. falciparum*) and from 2 cases of general paralysis inoculated with *P. vivax*. The blood was inoculated in various ways, chiefly subcutaneously and intravenously. He discusses the subject under the following headings :—incubation period ; attack ; under the latter he deals with, blood changes, parasitological picture, course of fever, special parasitological picture, mortality in experimental malaria, termination of experimental malaria, immunity in experimental malaria. He had only 4 deaths and only one of these could be certainly ascribed to the malaria treatment, giving a mortality of 0·39 per cent. He finds the immunity produced by inoculated malaria is not lasting and its grade varies with the strain employed. The paper should be read by those interested in malariotherapy. *E. D. W. Greig.*

WEISS (O. L.). Die Impfmalaria und ihre Kupierung durch Cardiazol-Chinin. [**Termination of Inoculation Malaria by Cardiazol-Quinine.**]—*Med. Klin.* 1932. Dec. 9. Vol. 28. No. 50 (1461). With 2 figs.

The use of cardiazol during the whole period of the course of malaria is recommended in place of digitalis to support the heart. Recently Knoll & Co. have prepared a combination of cardiazol and quinine, which is dispensed in ampoules (each ampoule contains :—0·1 gm. cardiazol and 0·25 gm. quinine lactate) and in sugar coated beans (each bean contains :—0·05 cardiazol and 0·1 gm. quinine hydrochloride). His observations were made on 52 cases of inoculated malaria. Two beans of cardiazol-quinine were given 5 times daily for 5 days and the results in terminating the fever were better than those with quinine alone. In other cases he gave 4 ampoules daily for 5 days with even better results due, in his opinion, to the combination of quinine lactate and cardiazol having a more intensive action. Where there is anxiety regarding the general condition of the patient and it is

desired to have only a moderate rise of temperature, then administration of 2 to 3 beans of cardiazol-quinine (0·1 to 0·15 gm. cardiazol and 0·2 to 0·3 gm. quinine) a few hours before the attack is expected is indicated; by this method a patient suffering from advanced aortic aneurysm was able to complete the course satisfactorily.

E. D. W. Greig.

SERGENT (Et.) & CATANEI (A.). Essais de filtration du virus du paludisme des oiseaux (*Plasmodium relictum*). [**Attempts to filter the Virus of Bird-Malaria.**]—*Bull. Soc. Path. Exot.* 1933. Feb. 8 & 9. Vol. 26. No. 2. pp. 267–268.

The experiments here described were made in connexion with the claim of ASCIONE and MARIOTTI that *P. vivax* is filterable [see above, p. 487]. The authors found that when the citrated blood of canaries containing numerous *P. relictum* was passed through Chamberland L 1, L 2, and L 3 candles, the infection was removed. *W. F.*

RUSSELL (Paul F.) & NONO (Andres M.). **Avian Malaria, VII. Plasmochin as a Prophylactic Drug in Sporozoite Infections of Avian Malaria.**—*Philippine Jl. Sci.* 1932. Dec. Vol. 49. No. 4. pp. 595–625. With 1 plate. [20 refs.]

The authors found that plasmoquine did not protect against sporozoite infection in avian malaria, whether the sporozoites were inoculated by mosquitoes or with a syringe. They conclude from their own experience, and that of others, that plasmoquine has no better claim than quinine to the title of prophylactic in human malaria.

Russell (this *Bulletin*, Vol. 29, p. 353) has already shown that, *in the inoculation of blood* containing *P. cathemerium* of canaries, infection of the recipients is regularly prevented by daily intramuscular injections of 0·00016 grams of plasmoquine. In this paper, its effect on sporozoite infections is investigated. Two birds were put into cages with infected *C. quinquefasciatus* (*fatigans*) for 5 days, and 0·0002 grams of plasmoquine were injected daily. Both birds became infected and died. Three birds put for one day into a cage containing mosquitoes infected with *P. capistrani*, became infected although they were given inoculations of plasmoquine both before and after exposure. The results were no better when quinoplasmine was used. Other birds were kept in the infecting cage for only a few hours, and were given plasmoquine injections, up to the maximum tolerated dose, before, in the middle, and at the end of the exposure, but they were not protected. A number of birds were inoculated with sporozoites by means of a syringe. Plasmoquine was given both before and after the inoculation, but there was no evidence of protection. The sporozoite emulsion was made by grinding up the thoraces of infected mosquitoes in salt solution. In another experiment, plasmoquine was added to the sporozoite-saline emulsion, and the mixture was left for 15 minutes before being injected into canaries. There was no evidence of protection, 3 out of 4 birds became infected. The authors conclude that neither plasmoquine, nor quinoplasmine, in the maximum doses which will not cause toxic symptoms, is a prophylactic against avian malaria when sporozoites are injected, either in saliva by mosquitoes or in saline mixtures by needle. *W. F.*

TATE (P.) & VINCENT (M.). **The Action of Plasmoquine on Mosquito-induced Malaria of Birds.**—*Parasitology.* 1933. Feb. Vol. 25. No. 1. pp. 96–101. [11 refs.]

Plasmoquine prevents or delays attacks of malaria in birds infected with *P. relictum* by direct blood inoculation, but has little or no prophylactic action in birds infected by the bites of mosquitoes.

Plasmoquine given in large doses to canaries before they were bitten, or for three days before and one after, had no prophylactic action in 3 out of 4 birds treated. Plasmoquine given daily for 6 days after mosquito infections, had no effect on the time of appearance of parasites. Though longer treatment prevented the appearance of parasites while it was continued, they appeared soon after it was stopped. On the contrary, very small doses of plasmoquine caused great delay in the appearance of parasites when the infection was by blood inoculation.

W. F.

RUSSELL (Paul F.). **Avian Malaria Studies, VIII. The Bleeding Time in Canaries : Normal and in Malaria.**—*Philippine Jl. Sci.* 1932. Dec. Vol. 49. No. 4. pp. 627–649. With 5 plates & 1 fig. [12 refs.]

The bleeding-time is often doubled in acute avian malaria.

Duke's bleeding-time test consists of blotting up on absorbent paper, at half-minute intervals, the blood which has flowed from a small cut in the ear. The duration of the haemorrhage is called the bleeding time. It is distinct from the coagulation time, and is not prolonged in haemophilia. The average bleeding-time in man is 2·5 minutes. The author examined canaries by pricking their legs with a Hagedorn needle. The average bleeding-time was only 42·4 seconds. In acute avian malaria, the B.T. was more than doubled in 52 per cent. of the birds. This prolonged B.T. coincides with, but is not necessarily caused by, a decrease in the red cells and the calcium content of the blood. *W. F.*

i. SINTON (J. A.) & MULLIGAN (H. W.). **Note on an Intradermal Reaction in Monkey Malaria.**—*Indian Jl. Med. Res.* 1932. Oct. Vol. 20. No. 2. pp. 581–583.

ii. —— & ——. **Studies in Immunity in Malaria. Part I. An Intradermal Reaction in Malarial Infections in Monkeys.**—*Records of the Malaria Survey of India.* 1932. Dec. Vol. 3. No. 2. pp. 323–345. With 4 plates. [14 refs.]

i. Infected monkeys gave a positive skin reaction when inoculated intradermally with an antigen prepared by digesting a suspension of malaria parasites with papain.

For the first few hours after injection, there was more swelling in the normal controls than in the infected monkeys but, after 3 or 4 hours, reaction commenced in the latter and within 24 hours there was a definite swelling 20 mm. in diameter, with central necrosis or petechiae ; meanwhile all swelling had disappeared in the controls. The more acute and severe the infection, the greater was the reaction.

ii. This is a more detailed account and good illustrations are given.

W. F.

ROW (R.), DALAL (N. P.) & GOLLERKERI (G. V.). **On the Value of Atebrin in Monkey Malaria.**—*Trans. Roy. Soc. Trop. Med. & Hyg.* 1933. Mar. 23. Vol. 26. No. 5. pp. 469–470. [10 refs.]

Atebrin did not cure malaria in two monkeys under experiment.

Infection in *Macacus rhesus* is almost always fatal. Two of them were inoculated with blood from an infected moribund monkey. On the day after parasites first appeared, they were each given 0·025 gm. of atebrin, and this treatment was continued for 4 more days. The parasites disappeared, but reappeared 12 days later. One was then given atebrin for 15 days, and the other for 5 days. Again the parasites disappeared, but in about 14 days they returned and the animals died. *W. F.*

WATSON (Malcolm). **Tropical Hygiene and Malaria Control on Mines at Various Elevations.**—*Bull. Inst. Mining & Metallurgy.* 1933. Jan. No. 340. 12 pp. With 6 figs. on 4 plates.

Alluvial mines and rice fields are usually free from malaria because the water is contaminated with silt. An example of malaria control on an Indian iron mine is given. On the Rhodesian copper mines, pools must be oiled and sites chosen far from swamps ; otherwise these must be drained.

The author gives a brief outline of the biology of the malaria parasite, and touches on the breeding places of mosquitoes. The old idea that for malaria to occur there must be a swamp and stagnant water is far from the truth. The most extensive swamps in which people live are rice fields, but thousands of square miles of them in India, Malaya, Siam, the Philippines and Java are almost entirely free from malaria, so too are the silty swamps round tin mines. The reason is that most malaria-carrying mosquitoes choose clean water, and will not breed in the contaminated water of mines and rice fields. The tin mines of Malaya lie between sea level and 1,000 feet. They are usually free from malaria because the water in the surrounding swamps is contaminated by the tailings from the mines. Some which have small streams running near them are very malarious, but the disease can be controlled by oiling. The iron mines in India, at an elevation of 500 to 2,000 feet are intensely malarious in the monsoon, when there are many springs. Work at the Noamundi mine was almost brought to a standstill by malaria which originated in a stream running down the centre of the area. When this and its branches had been controlled, the mine became healthy. The copper mines of Northern Rhodesia lie at an elevation of 4,000 feet ; the carriers are :—(1) *A. costalis* which lives in pools in the sunshine, and can be dealt with by regular oiling, and (2) *A. funestus* which breeds in the grass-grown swamps, known as dambos, where drainage is necessary to control them. The camps should be pitched as far as possible from extensive dambos. *W. F.*

BARROWMAN (Barclay). **An Example of Antimalarial Subsoil Drainage under Rural Conditions.**—*Malayan Med. Jl.* 1932. Dec. Vol. 7. No. 4. pp. 116–118. With 1 fig.

Several speakers at the annual meeting of the Malayan Branch of the B.M.A. (this *Bulletin*, Vol. 29, p. 335) expressed doubt as to the suitability of subsoil drainage for rubber estates. The author gives an outstanding example of its success in such an area.

Seafield, the estate in question, " is situated within a belt of territory which is probably amongst the most malarious spots in the world." During the first fourteen years following the installation of subsoil drains :—" The malaria incidence was reduced from 939 per cent. per annum to 1 per cent. per annum. . . . This record alone gives ample

evidence of how effective was the work of malaria control, which depends for its success on drainage alone. . . . The total contribution of the Company to anti-malaria schemes from 1910 to 1932 on the estate, amounts to nearly a quarter of a million dollars or £30,000." It is calculated that the alternative scheme of open drains and oiling would have cost some £700 a year more than the subsoil drains.

W. F.

BARROWMAN (B.). **A Note from an Estate Medical Practice in Malaya.** —*Indian Med. Gaz.* 1933. Feb. Vol. 68. No. 2. pp. 92–102. With 1 map, 13 charts & 1 fig.

The author has been associated for the last eleven years, first as an assistant and later as principal, with the practice founded in 1908 by Sir Malcolm WATSON whose methods of malaria control he follows with but little alteration. *A. ludlowi*, the brackish water breeder of the coastal belt, is dealt with by bunding and the provision of drainage through tide-gates. *A. umbrosus*, of the flat land, is controlled by concentrating all water in clean-cut channels, free from vegetation and open to the sunlight. *A. maculatus* of the hilly country is also dealt with by concentrating all water in well-defined channels ; either subsoil, open concrete, or earth drains. The latter require oiling. It is mentioned, as a warning, that on one estate where the subsoil pipes became blocked and water seeped to the surface, oiling was used with disastrous effect ; for when the pipes were cleared, the oily earth above them formed an impervious covering which had to be removed before drainage could be effected. Another important point is that subsoil drains cannot carry off storm water. The ravines must therefore be levelled and graded in order to allow the surface water free passage to the open drains. As an example of the success of antimalaria drainage, in an area cut off by water from contaminating influences, the author tells the story of Carey Island, which is situated at the mouth of the same river as the notorious Port Swettenham. Malaria control on Carey Island was begun when it was cleared for rubber planting ; it consists of deep drainage, careful supervising of tide-gates and the siting of all housing at least half a mile from uncontrolled areas. The potential vectors are *A. ludlowi* and *A. umbrosus*. No oiling has ever been done. The population is about 5,000 ; 17,000 acres are under cultivation. The malaria incidence over the last 12 years has been less than 1 per cent. per annum. *W. F.*

WHITE (R. Senior). **Notes on a Brief Tour in Malaya.**—*Indian Med. Gaz.* 1932. Dec. Vol. 67. No. 12. pp. 683–690. With 15 figs. and 1 diagram.

The author deals with the impracticability of the general application of Malayan methods to India, with the more recent developments of subsoil drainage, and with the biological control of *A. maculatus*.

The first thing which struck him was that conditions in Malaya were quite different from those in India. He saw few Malays ; it was not a problem of scattered villages, but a problem of industrial and urban malaria ; to subject Malayan methods to criticism based on an Indian viewpoint seemed futile. He was also struck by the sharp limitation of each of the three carriers to its own particular zone ; *A. ludlowi* to the tidal, mangrove flats, *A. umbrosus* to the jungle of the lowlands, *A. maculatus* to the hills. He found that subsoil drainage had undergone

several modifications since the early days ; the pipes are now laid 5 feet deep instead of 18 inches. The herring-bone layout has given place to a central pipe with hill-foot laterals leading into it at intervals. The surface water is no longer carried underground by the central subsoil drain, but is taken off by an open drain laid above it. The expense is heavy ; the pipes get blocked with roots, and must be taken up and cleaned ; the grass in the ravines must be cut [this cannot be cropped by cattle, as the author suggests, because *A. maculatus* will breed in the hoof-marks] ; trees must not be grown near the drains, and this may involve the sacrifice of 4 or 5 per cent. of the rubber trees on an estate. In all, the annual upkeep charges amount to 5 per cent. on the capital outlay. The author was particularly interested in the " biological control " of *A. maculatus*, by Professor WILLIAMSON, in the sanatorium area known as Cameron's Highlands. Here, by means of a set of tree-trunk dams, a *maculatus* breeding stream was converted into a series of pools with minature waterfalls. Manure and leaf mould were put into these pools, water plants (*Nymphaeaceae* and *Utricularia*) were introduced, and now *A. maculatus* no longer breeds there, but only *A. sinensis* and *A. barbirostris*. *W. F.*

CRAWFORD (R.). **Economy and Antimalarial Oiling.**—*Malayan Med. Jl.* 1932. Dec. Vol. 7. No. 4. pp. 112–115. With 2 figs.

It is suggested that the lower portions of streams, where the flow is slower and where oil coming down from the upper reaches tends to accumulate, do not need oiling so often as the more swiftly running streamlets near the source. For example, every 7 days at the head of the stream, and every 10 days lower down may be sufficient. Experiments are described which show that the substances passing into solution from the oil are of little importance, and that larvicidal action depends on the presence of a film. Exposure to an oil film for one hour caused the death of practically all larvae. Some 25 to 50 per cent. of anti-malarial oil can be recovered, for using again, if a boom is erected at a suitable site completely interrupting the water surface, and projecting some distance above and below it. *W. F.*

IREDELL (A. W.). **An Account of Mosquito-Proofing carried out by the Royal Air Force in India.**—*Proc. Roy. Soc. Med.* 1932. Nov. Vol. 26. No. 1. pp. 1–5 (United Services Sect. pp. 1–5). Also in *Jl. Roy. Army Med. Corps.* 1933. Jan. Vol. 60. No. 1. pp. 33–37.

The author demonstrates the reduction in malaria which followed mosquito-proofing of R.A.F. stations in India.

Col. HANAFIN, I.M.S., reported in 1928 on the mosquito-proofing of one of two sets of barracks at Lahore. The incidence of malaria per 1,000 for the years in which the barracks were unproofed was 850, 483, and 568 ; for two years after proofing, it was 182 and 46. The incidence in the control, unproofed barracks nearby was, 594, 307, 470, 672, and 266. The author's observations concern the mosquito-proofing of the R.A.F. stations at Karachi and Kohat. In the following table the figures in dark type show the incidence per thousand after the buildings had been proofed with gauze consisting of 90 parts of copper and 10 of zinc. Antimosquito measures were impracticable, since a prolific breeding area, close to the station, was on private land and could not be touched.

TABLE A.—Malaria (Primary) at R.A.F. Stations, India.

Station.	Average strength.	Case Incidence per 1,000.						
		1925	1926	1927	1928	1929	1930	1931
Karachi	729	99	142	183	44	**32**	**20**	**10**
Kohat	188	149	378	183	150	280	**167**	**57**
Ambala	146	119	124	104	37	30	26	91
Lahore	146	118	261	187	21	150	90	87
Peshawar ...	164	85	214	126	39	180	50	6
Quetta	231	17	233	40	46	85	46	125
Risalpur ...	247	61	139	85	15	189	57	39

The sea-breezes filled the meshes of the gauze with sand. Gentle hosing cleaned it more satisfactorily than scrubbing with hard brushes. The lower 5 feet of the gauze was protected with ordinary 1 inch wire netting. The men were most emphatically and unanimously in favour of mosquito-proofing as opposed to mosquito-nets. The cost, at Karachi, was £8,300, and at Kohat, £3,700. Money was not available for proofing other stations. *W. F.*

EARLE (Walter C.). **Some Observations of Antimosquito Screening and Screening Materials.**—*Puerto Rico Jl. of Public Health & Trop. Med.* 1932. Dec. Vol. 8. No. 2. pp. 227–234. [Spanish version pp. 235–242.]

The author directed a current of air from an electric fan on an anemometer, and on wet- and dry-bulb thermometers. He then placed samples of wire gauze between the fan and the instruments, and noted the amount of obstruction.

Data on Obstruction to Wind Caused by Various Types of Screens—Using Electric Fan as Source of Wind.

		Without Screen	1 16 Mesh copper ·01 in. wire	2 16 Mesh copper ·015 in. wire	3 16 Mesh bronze ·015 in. wire	4 16 Mesh bronze ·01 in. wire	5 16 Mesh copper ·01 in. wire	6 16 Mesh Monel metal ·009 in. wire	7 12 Mesh galv. wire	8 Cotton cloth screen 16 mesh
I. With Anemometer	Screen at right angle to direction of wind ...	10	6	5	5·5	6	6·5	7·0	8·5	2·5
	Screen at 45° angle ...			6·5	6·5	6	6·5	7·0	8·5	6·5
II. With Thermometer	Screen at right angle to direction of wind ...	35	35	52	48	35	35	38	40	60
	Screen at 45° angle ...		35	43						40

I. Numbers represent velocity of wind in miles per hour.
II. Numbers represent time in seconds necessary to reduce temperature of wet bulb to minimum.
Dry temperature at beginning 85. Wet=78·5.
Dry temperature at end of experiments 87·5. Wet=78·8.

The objection is frequently raised that screening interferes with ventilation and makes a house hotter. The table shows that metal screens of coarse mesh reduce the velocity only about one-third, and that there is no appreciable difference in the rate of lowering the wet-bulb thermometer. Cloth screens gave very bad results.

A great advantage of screening is that it makes the stuffy mosquito-net unnecessary. Galvanized iron screening, 12 mesh, 0·015 wire is satisfactory for use several miles inland, but it lasts only a few months where it is exposed to sea-breezes. Near the sea, the more expensive bronze, or Monel metal, wire must be used. *W. F.*

ACHUNDOW (I.). Ueber den heutigen Stand der Malariabekämpfungsfrage in Aserbaidjan. [**Present Position of Antimalarial Measures in Azerbaijan.**]—*Arch. f. Schiffs- u. Trop.-Hyg.* 1933. Mar. Vol. 37. No. 3. pp. 136–141.

The author gives an account of malaria, principles of antimalarial measures, organization and results of antimalarial campaign, and further plans and schemes for antimalarial operations, in the Republic of Azerbaijan (in the eastern part of the Transcaucasus).

Malaria plays a very important rôle in the diseases of the country; thus in recent years the spleen index varied from 25·7–52·4 per cent.; the parasitic index from 6·5–22·4 per cent.; and the Ross index from 1·5–3·4 per cent. The principle of the antimalarial measures is a combination of the Koch and Ross methods carried out simultaneously. The antimalarial organization consists of:—(*a*) A central Transcaucasian malarial committee. (*b*) A malarial committee for the Republic. (*c*) A tropical institute at Baku. (*d*) At the periphery, malarial tropical stations, posts and sections. On antimalarial measures in Azerbaijan the following amounts were expended, in 1930, 435,000 roubles, in 1931, 1,327,300, in 1932, from 3,353,000–5,281,700. The further plans for antimalarial operations include quinine prophylaxis, small bonification schemes and later the carrying out of large drainage schemes in swampy areas. *E. D. W. Greig.*

FIGUEIRA (L.) & LANDEIRO (F.). Estação experimental de Benavente: relatório do primeiro ano de luta antisezonática (1931). [**Antimalaria Measures at Benavente (Portugal) in 1931.**]—*Arquivos Inst. Bact. Camara Pestana.* 1932. Vol. 6. No. 3. pp. 191–243. With 22 figs. & 1 plate. French summary.

BÔTO (Rodrigo). Addenda. Resultado das observações efectuadas nos concelhos de Benavente e Salvaterra de Magos sôbre a distribuição da "Gambúsia" e a sua provável procedência.—*Ibid.* pp. 245–249. With 1 map.

Benavente has an area of 2,880 hectares [nearly 7,200 acres] of which 100 are occupied by surface water and 95 by rice fields. This article gives a detailed account of the prevalence of malaria, the investigations carried out at the experimental station during the first year of its inauguration and the measures taken to deal with the conditions found.

The prevalence of infection varied greatly according to the time of year. Among 208 school children examined in April the percentage of

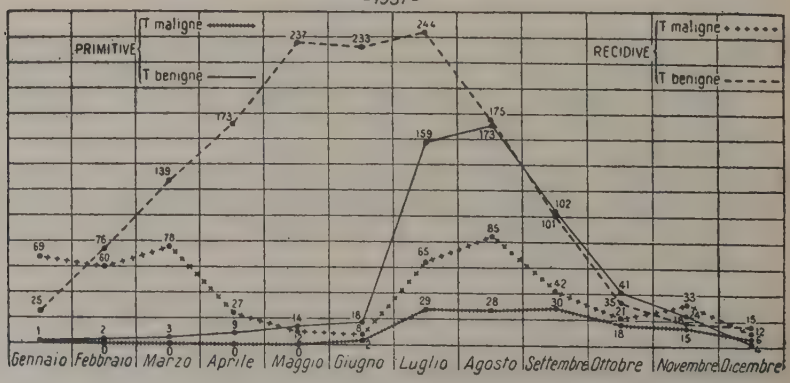
infection was 30·7 ; in November among the same number only 3·9 ; the splenic indexes at the same times were 23·5 and 3·1 per cent. respectively. Among 2,930 presenting themselves for consultation more than half (58·8 per cent.) showed parasites ; 48·9 per cent. were *P. vivax*, only 5·2 *P. falciparum* (excluding 1·2 per cent. in whom both were present), and 0·7 *P. malariae* ; 3·8 per cent. were not identified.

The water-collections were treated with Paris green, distributed by aeroplane. Gambusia was extensively employed also. Of 71,663 mosquitoes captured the proportion of Anopheles to Culex was 26 : 1. 2,089 individuals received treatment.

The article is well illustrated by photographs showing the conditions of the terrain before and after treatment. *H. H. S.*

PECORI (G.) & ESCALAR (G.). Relazione sulla campagna antimalarica nell'Agro Romano durante l'anno 1931. [**The Antimalaria Campaign in Agro Romano during 1931.**]—*Riv. di Malariologia.* 1932. Vol. 11. No. 5. 63 pp. With 15 figs. (1 map).

The report opens with an account of the organization and enumerates the various health depots—8 suburban, 28 permanent stations in Agro Romano and 2 of a temporary nature. A map is reproduced showing by depth of shading the prevalence of infection in the various districts. The population is given as 79,708 of whom 31,392 are floating (nomadi) and 43,316 permanent. The numbers infected or suffering from attacks during the year are stated : of 641 cases of subtertian malaria 129 were first attacks and 512 relapses ; of 2,021 benign tertian 550 were first attacks and 1,471 relapses ; there were 23 quartan, 4 being first attacks. In all three the figures were lower than in 1930, namely 253 less subtertian, 470 benign tertian and 7 quartan, the grand total being 2,685 in place of 3,415 and the percentage infection 3·2, the lowest in the table of records giving the returns since 1924.



Showing monthly prevalence of benign and malignant tertian infections in Agro Romano during 1931, distinguishing first attacks (primitive) from relapses (recidive).

[Reproduced from the *Rivista di Malariologia.*]

Next follow details of infection among the permanent and nomadic population and a diagram showing very graphically the monthly prevalence of the benign and malignant tertian infections.

Of 5,627 children in the rural school 383 had enlarged spleens, 6·8 per cent. as compared with 7·6 in 1930.

The last section of the report deals with antimalaria measures such as the treatment of patients, antilarval campaigns, bonification on a small scale and zooprophylaxis. There are appended many tables with details of population and infection rate of the various localities in the larger districts. *H. H. S.*

FISCHER (O.) & GÜNSBERGER (O. D.). Ueber die Ursache der positiven Wassermann-Reaktion bei Malaria. [**The Cause of the Positive Wassermann Reaction in Malaria.**]—*Ztschr. f. Immunitätsf. u. Experim. Therap.* 1933. Vol. 78. No. 3/4. pp. 295–307. [20 refs.]

The authors detail the results of their experimental research to prove their proposition that the positive W.R. given by serum from malarial cases is caused by the reaction of erythrocyte lipoids with homologous antibodies.

They found 21 sera out of 28 from malarial cases gave definite to complete positive complement fixation with erythrocyte extract; five hundred Wassermann negative sera from healthy and sick persons gave, with few exceptions, negative reactions. Of 60 Wassermann positive sera some reacted also with the erythrocyte antigen, but they could be easily distinguished from the malarial sera if the quantitative behaviour was taken into consideration. An ox heart extract relatively poor in erythrocyte lipoids is described, and although a good syphilitic antigen, with malarial sera it either did not react or only relatively weakly. If the W.R. is carried out with erythrocyte extract also, then the Wassermann positive reactions in malaria can be certainly differentiated from those of syphilis, which is of considerable practical importance in malarial districts. *E. D. W. Greig.*

PESOPOULOS (Spiro). Ueber eine gastralgische Form von Malaria mit Mundaphthen. [**A Form of Malaria with Gastralgia and Aphthae of the Mouth.**]—*Arch. f. Schiffs- u. Trop.-Hyg.* 1933. Feb. Vol. 37. No. 2. pp. 69–72. [11 refs.]

The case of a young man who for more than 3 years had suffered regularly every 40 days with fever lasting 8–12 days accompanied by gastralgia and aphthae; cure was effected by an intensive course of quinine. Malarial parasites were not found. *A. G. B.*

GIGLIOLI (George). **Quartan Malarial Nephritis and Malarial Haemoglobinuria as Family or House Diseases in the Interior of British Guiana. Field Observations on the Epidemiology and Etiology of Blackwater Fever.**—Davson Centenary Fund—British Guiana Gold Medal Award, 1932.—32 pp. With 2 charts. [15 refs.]

The conclusions reached by the author as the result of these investigations have already appeared in this *Bulletin* under the heading of Blackwater Fever, see page 97, above. *W. F.*

MONTGOMERY (W. M.). **Sulphur as a Prophylactic in Malaria.**—*South African Med. Jl.* 1932. Dec. 10. Vol. 6. No. 23. pp. 771–772.

The daily ingestion of sulphur in quantity "sufficient to give a pronounced odour to the sweat" acts as a prophylactic. *W. F.*

SMITH (Claude R.). **The Specificity of the Kahn Test in Malaria.**—*Jl. Lab. & Clin. Med.* 1933. Jan. Vol. 18. No. 4. pp. 396–398.

The author concludes that malaria infection has no effect upon the results of the Kahn test. *W. F.*

AUBRY & DUMOLARD. Comment il faut concevoir le paludisme chronique au point de vue clinique.—*Arch. Inst. Pasteur d'Algérie.*—1932. Sept. Vol. 10. No. 3. pp. 342–344.

BARRAUD (P. J.). *Anopheles aitkeni* James var. n. *pinjaurensis.*—*Records of the Malaria Survey of India.* 1932. Dec. Vol. 3. No. 2. pp. 353–355. With 6 figs.

BENHAMOU (E.) & NOUCHY (A.). A propos de trois cas d'ictère hémolytique paludéen.—*Bull. Soc. Path. Exot.* 1933. Mar. 8. Vol. 26. No. 3. pp. 423–425.

BENHAMOU (E.) & ODRY. Purpura palustre.—*Bull. Soc. Path. Exot.* 1933. Mar. 8. Vol. 26. No. 3. pp. 420–422.

BONFA (A.). The Life-Cycle of Malaria Parasites in Human Blood.—*South African Med. Jl.* 1932. Dec. 24. Vol. 6. No. 24. pp. 796–801.

BOOKER (C. G.) & ANNECKE (S.). The General Practitioner in the Prevention of Malaria.—*South African Med. Jl.* 1933. Feb. 11. Vol. 7. No. 3. pp. 79–84.

BROTZU (Giuseppe). La profilassi medicamentosa della malaria nel campo pratico.—Reprinted from *Bull. d. Sci. Med.* 1932. 7 pp.

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COVELL (G.). A Further Note on Malaria in Patiala State.—*Records of the Malaria Survey of India.* 1932. Dec. Vol. 3. No. 2. pp. 271–278. With 1 map.

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We record with much regret the death on June 7th of Sir WALTER MORLEY FLETCHER. Sir Walter was the representative of the Medical Research Council on the Managing Committee of the Bureau from September 1924.

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